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A RARE ANOMALY IN THE ELBOW — PATELLA CUBITI[1]

by

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Roentgenology has greatly increased our knowledge of skeletal anomalies. While there in pre-roentgen times were only a few reports of findings of an accessory bone embedded in the triceps ligament, chance findings in anatomical preparations, the number of similar observations has increased considerably since the use of roentgen rays has become widespread. While so-called accessory bones are frequent in the skeleton of the hands and feet, their presence in the elbow must be regarded as a rarity. The first report of a sesamoid bone at the posterior part of the elbow region is that of PFITZNER. The first roentgen observation of a similar bone was made by KIENBÖCK in 1903 and since that time the number has increased to 15.

Own Cases

Case 1. A 51-year-old washer woman. No skeletal anomalies in the family. As small child she injured the left elbow and had subsequent slight pains. No medical treatment. 10 years ago a slight injury of the same elbow. Has been at work ever since but elbow has been bothersome. Has had »rheumatism» for many years but without predilection for the elbow.

4 days before roentgen examination slight injury of the left elbow with increased pains in the joint. These have since decreased.

General examination revealed nothing of significance.

Left elbow: posteriorly there was a visible change in contour as the olecranon protruded markedly. Actually there was above the tip of the olecranon an ossified protrusion, separated from the olecranon by a distinct slit. This ossification was more prominent when the elbow was bent and was quite insensitive. Extension was possible up to within 20° of completion, and it seemed that it was this extra piece of bone which mechanically prevented further extension. Supination was slightly limited. Normal strength. No pain accompanied joint movements. The triceps ligament had a fan-shaped attachment on the

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dorsal surface. In the furrow between the olecranon and the elbow cap there were fibrous connections.

Under translumination the extra bone was seen to move with the olecranon from maximum flexion to mid-position. From mid-position to maximum extension the upper corner moved in a volar direction and finally stood with its longitudinal axis perpendicular to the longitudinal axis of the ulna (see Fig. 1).

The roentgenogram shows, above the olecranon which is 3 mm shorter than on the other side, the $3.4 \times 3.4 \times 1.5$ cm large bone which resembles the patella genus. It is this which causes the abnormal configuration so that there are two prominences on the extensor side of the joint, like the patella and tibia condyles of the knee. It shows normal bone contours and a rather broad corticalis. The upper part faces toward the fossa olecrani, the lower part toward the olecranon. The axial picture shows a prominence in the middle of the anterior surface, as on the patella genus. There can be no doubt that the anterior surface is covered with cartilage. The bone slides without friction with a circular movement with gradually diminishing radius over the upper part of the trochlea into the fossa olecrani, where the upper corner bends toward the humerus and further extension is prohibited.

Arthrography (Fig. 2) with 20 % per-abrodil shows that the joint cavity extends a considerable distance beyond the upper limit of the elbow cap, resembling a recessus superior genus. Contrast between the olecranon and the patella cubiti can be seen. Moreover there are roentgenological indications of arthrosis deformans.

Case 2. A 73-year-old man. No skeletal anomalies in the family. Had always been healthy and at work, except for »rheumatism» the last few years with no predilection for the elbow joints. Three weeks previously a slight injury of the left elbow. Slight pains. Continued at his work. No previously known injuries. General examination revealed nothing of significance. Left elbow: slightly limited extension and supination. Between the tip of the olecranon and a bone lying above it, a furrow could be palpated; this bone protruded markedly.

Examination of the rest of the skeleton revealed no abnormalities. A roentgenogram of the left elbow revealed just above the olecranon, which was somewhat shorter than normal, a $3.5 \times 3 \times 1.5$ cm chestnut-shaped bone, which closely resembled the patella. It was embedded in the triceps ligament and in the joint connection partly with the superior surface of the olecranon and partly with the humerus. The anterior surface was slightly concave, even and smooth and resembled a joint surface. The fossa olecrani was deeper than on the other side. Moreover there were roentgenological indications of arthrosis deformans. As the roentgenogram was identical to that of Case 1 we refer to Fig. 1. The right elbow showed no abnormalities.

A review of earlier published cases is of interest. In the 3 first cases (PFITZNER, CHENAL, TILLESEN) there was a bone with no cartilage covering on the anterior surface embedded in the triceps ligament. In the roentgen literature there are 2 similar cases (GRAUER, WINCKLER). In a clinical and anthropological study of the foramen supratrochleare (HIRSCH) it is mentioned that a small bone nodule is sometimes found in this foramen. VIRCHOW has observed a similar case. When KIENBÖCK in 1903 described the first roentgenological observation of patella cubiti — the designation is his — he says that including VIRCHOW's case there have in all been reported 5 cases up to that date. KIENBÖCK's case was bilateral, the patella cubiti were about the same size as in our cases and in

Fig. 1 a. Fig. 1 b. Fig. 1 c.

Fig. 1. Patella cubiti. The dorsal surface where the triceps ligament is attached, the smooth and probably with cartilage covered anterior surface. Arthrosis deformans 3 different phases of the joint movement.

general agree well with these. While KIENBÖCK in this first case believes it to be a skeletal anomaly, in a later publication (1914) he tends toward the interpretation that it may be a pseudo-arthrotically healed olecranon fracture. KATZ (1915) is also of this opinon.

In 1918 PAULY reports on a bilateral case, treated on the left side as a fracture with osteosuture. A control examination revealed a similar anomaly on the other side. On both sides there was a piece of bone embedded in the triceps ligament which both in form and structure resembled a patella genus.

Fig. 2. Arthrography. Posterior extension of the joint cavity. Contrast between the olecranon and patella cubiti.

In 1928 BEYKIRCH published another bilateral case, very similar to PAULY's, with a normal olecranon on the one side, and somewhat shorter on the other. The same year EWALD reports an operated case. No trauma. The bone was 5×3 cm, deeply embedded in the triceps ligament and connected with the later just like the patella genus with the quadriceps ligament and had to be removed radically. The anterior surface was covered with cartilage. The joint cavity was enlarged posteriorly and was

attached lower down on the ulna than usual, on a prominence. The cartilage was not examined microscopically, which ROSTOCK did in a case which he operated. He found true hyaline cartilage. KREMSER's case (1934) was also without any known trauma in the case history and was discovered by chance in a dyspeptic patient. Still 3 more cases have been reported (JAPIOT, GUNN, ODESSKY and MELNIKOWA).

The most recent case reported in the literature is that of KIENBÖCK and DESENFANTS (1937). This was a case of a familial anomaly which was bilateral in the son, unilateral in the father. There were no other cases in the family. The son's case was similar to ours while the father's was more a »forme fruste» with a very fine cleft between the olecranon and the elbow skeleton. Roentgen examination revealed in both a chestnut-shaped and chestnut-sized bone, embedded in the triceps ligament and in joint connection with the humerus. Both had a somewhat stubby but otherwise normal olecranon.

In all, 15 cases have been reported, but 4 of these are doubtful. All the 11 certain cases show good agreement, with the same knee-like deformity in the elbow, the majority have limited extension, some have slight, others no traumata, the size of the extra bone is very regular, the anterior surface has joint connections with the humerus and the olecranon and during movement it turns into the fossa olecrani. The posterior surface serves as place of attachment for the triceps ligament. Several of the cases show the changes characteristic for arthrosis deformans, and it must be assumed that these joints, because of the anomaly, are predisposed for this affection. The condition has not been particularly bothersome, has seldom interfered with work, even after injuries.

In our cases it has not been possible to examine the families. Case 2 was examined by a physician in the patient's native district who sent me his roentgenogram for examination.

The time of appearance of the olecranon's epiphyseal process is claimed to be from 2 to 12 years. It is sometimes double, the one somewhat above the other. Ossification with the ulna diaphysis occurs between 16 and 20 years of age. On roentgenograms the epiphyseal anlage is visible between the 10th and 13th years, sometimes there are 2 or more (KÖHLER). It is thus reasonable to assume that one of these develops into the olecranon, possibly somewhat reduced in size, while the other develops into a patella cubiti, or, to use a better name, os ephiphyseos olecrani. The not so rare extra olecranon trace may have the same origin. Several authors are of this opinion (BEYKIRCH, EWALD). Others prefer the explanation of a pseudo-arthrotically healed olecranon fracture (KIENBÖCK, KATZ, GUNN).

Our 2 cases as well as most of the others in the literature do not present good evidence of traumatic origin. The once demonstrated familial

occurrence and the 4 bilateral cases do not point in that direction. The interpretation of the anomaly as a true sesamoid bone in the triceps ligament which originates from an abnormality in the embryonic anlage seems to be the most likely. From a purely clinical standpoint there is little to indicate that fracture is the cause. In our one case where arthrography was carried out, the observation of a recessus superior-like extension of the joint cavity does not point in the direction of traumatic origin.

It is a question whether the patella genus corresponds to the olecranon. Several authors believe they are homologous, and HYRTL states that they may well be compared: the patella genus is thus a free and independent olecranon, an olecranon mobile. The olecranon has also been called olecranon fixa.

There are many variants in the patella. In this connection patella partita should be mentioned, also the occurrence of a patella superior, which is found in rodents. The presence of such a patella superior makes the assumption of the origin of patella cubiti on the basis of a double epiphyseal anlage more likely, also on the basis of an embryonic abnormality.

In the animal kingdom the lowest stages at which the triceps ligament is so well developed that patella cubiti can occur, are in the frog (pipa) and the lizard (lacertilia). In the latter it has two parts, a proximal and a distal nucleus. Birds may have one or two elbow caps, and bats, insect eaters, rodents and one of the edentates (manis) also have patella cubiti.

The theory has been advanced that the elbow cap may arise from the olecranon by means of sloughing off of a piece of bone (Abgliederung). In pipa and lacertilia the olecranon is so rudimentary that sloughing off would be impossible, nor can such a process be observed ontogenetically. According to NAUCK this sloughing off theory does not hold. The general opinion is summed up in NAUCK's words as to this theory: »Von diesem Gesichtspunkt aus erscheint uns die Patella cubiti aus der Leistung der Sehne und ihrer Beanspruchung heraus verständliche Bildung.«

Compare the occurrence of patella cubiti in the above mentioned animals and classes. It is possible that a more extensive investigation of higher mammals and apes would reveal a much more frequent occurrence of patella cubiti than in humans, which would make an atavistic origin seem more probable. The occurrence of patella cubiti in the higher theromorphs, a reptilian group which became extinct during the Jurassic period and from which our higher mammals probably descend, is of interest.

SUMMARY

Two cases of patella cubiti (os epiphyseos olecrani) are described. The roentgenograms show a small bone embedded in the triceps ligament, with a probably cartilage covered anterior surface and in form very similar to the patella genus. Arthrography in one case reveals a recessus superior-like extension of the joint cavity. An embryonic abnormity is assumed to be the cause.

ZUSAMMENFASSUNG

Es werden zwei Fälle von Patella cubiti (Os epiphyseos olecrani) beschrieben. Die Röntgenbilder zeigen einen kleinen Knochen, in die Trizepssehne eingelagert, mit wahrscheinlich knorpelbekleideter Vorderfläche und inbezug auf seine Form der Kniescheibe sehr ähnlich. Arthrographie zeigt bei dem einen Falle eine an den Recessus superior erinnernde Ausbuchtung der Gelenkhöhle. Als Ursache wird eine embryologische Missbildung angenommen.

RÉSUMÉ

Il est référé ici 2 cas de patella du coude (os epiphyseos olecrani). Les radiographies montrent un corps osseux incorporé dans le tendon du triceps, avec une face antérieure vraisemblablement cartilagineuse et d'une forme qui rappelle d'une manière frappante le patella du genou. L'arthrographie dans un des cas présente une dilatation de la cavité articulaire ressemblant au recessus supérieur. Une anormalité embryonnaire est supposée en être la cause.

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AN ATTEMPT AT THE ROENTGENOLOGIC VISUALIZATION OF CORONARY BLOOD VESSELS IN MAN[1]

by

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Visceral angiography was first introduced to medical science through the publication of EGAS MONIZ, in 1927, when he described a method of visualizing the blood vessels of the brain. Since then, the same principles of examination have been applied to an ever-increasing number of the deep blood vessels.

The aorta abdominalis and its branches to the abdominal organs were made opaque to roentgen rays by DOS SANTOS, LAMAS & CALDAS in 1929. Two years later, EGAS MONIZ, DE CARVALHO & LIMA introduced arteriographic examination of the pulmonary blood vessels by Forssman's technique, and in 1936 NUVOLI opacified the aorta thoracalis. Finally, in 1938, CASTELLANOS, PEREIRAS & GARCIA, and ROBB & STEINBERG succeeded in outlining all the chambers of the heart and the great central vessels.

The major part of the human circulatory system has thus been made available for intravital exploration. There still exists, however, an important part of the visceral vascular system which lies outside the scope of the angiographic technique, namely, the coronary blood vessels.

These vessels have already been the subject of roentgenographic study in the living subject. Thus, in coronary sclerosis, mural calcareous deposits, in some instances combined with regional pathologic changes in the outline of the myocardium, have been described (R. LENK, 1927). While precipitation of calcium can occur in atheromatous coronary arteries with unimpaired function, a secondary circumscribed change in the contour of the heart and the amplitude of contractions, in coronary thrombosis, seems to be of more significance from the diagnostic point of view (LEVENE & REID, 1932).

[1] Submitted for publication, April 11, 1945.

Fig. 1. Visualization of coronary arteries in the rabbit.
(After P. Rousthöi, 1933.)

Provided the intervention could be done without undue risk for the patient the visualizing of these vessels would serve as a further aid in the roentgen diagnosis of diseases of the coronary vessels.

It is obvious that direct puncturing of coronary arteries is a serious intervention involving risk for the patient's life, and it should therefore not be done merely in the interests of diagnosis. A more suitable measure seems to be to place the radiopaque substance, after puncturing, in the blood cistern from which these arteries are fed, in other words, in the bulb of the aorta. Working on the basis of this reasoning, P. Rousthöi in 1933 was able to demonstrate that opacification starting from the ascending aorta was possible in different animals. (See fig. 1.)

Having confirmed, in the dog, the observations of Rousthöi the next step of the present author was to apply the experiences gained with animals to man.[1] In this connection, a number of technical problems arose, most of which were finally overcome.

As far as the technique of injection is concerned, it was already known that Nuvoli had punctured the ascending aorta through the sternum without complications. As Nuvoli's paper was only available in the form of a short review the details of his method are not known. His object was to study an aneurysm on the aortic arch by arteriography, and there is thus reason to presume that he endeavoured to visualize this segment of the aorta in particular.

The method I employed was briefly the following.

Technique

1. A careful roentgenoscopic investigation of the topography of the ascending aorta is made in each case, the optimal direction of injection being marked, with the patient in the sitting position.

2. With the patient in the horizontal position perforation through

[1] Dr. H. Fröderberg, head physician of Vipeholm Hospital, Lund, Sweden, gave me invaluable assistance in my work.

the sternum with the apparatus commonly used for sternal puncture is carried out under local anesthesia. The puncture is made in the mid-line through the manubrium sterni, in a dorso-caudal direction. When the retrosternal topography is normal the perforation cannula reaches the loose fatty and connective tissue in the anterior mediastinum without coming into contact with the lung or the pleura.

3. Roentgenoscopic control of the position of the cannula point, with the patient seated, and if necessary, correction of its position.

4. After removal of the plunger in the apparatus to be used for injection a needle having an outside diameter of 1.5 mm. is inserted through the cannula, the patient sitting in a comfortable position while this is being done. The needle passes readily down to the ascending aorta, the pulsations of which can be distinguished. The fact that a continuous flow of blood is obtained proves that the point of the needle has passed through the wall of the aorta.

5. A Record syringe containing the contrast substance (thorotrast) is then connected and 20—30 ml. of the liquid is injected as rapidly as possible. During the injection a number of roentgen films are exposed. The average duration of exposure is 0.06 seconds.

6. After the conclusion of the exposures the patient lies in a horizontal position for one hour. Fluoroscopic examination of the thorax is then made. If circumstances permit, the patient can then get up.

Results

Puncture of the aorta using thorotrast as the contrast substance and the technique described above was carried out in 5 instances. The first two injections were made *pro exercitio*, without simultaneous roentgen exposures. The best result obtained so far is illustrated in figure 2, in which the bulb of the aorta, filled with contrast medium from a needle in the optimal position, can be seen. The aortic valves are clearly distinguishable.

In the area where coronary vessels would normally be expected with this projection, i. e. the area between the arrows, caudoventral to the bulb, the faint outlines of vessels are to be seen. These possibly represent the proximal segments of coronary vessels; they do not appear in views taken with the same projection without the use of contrast substance. The weakness of the contrast shadow, however, makes it difficult to differentiate between these vessels and the branches of the pulmonary veins which are projected over the silhouette of the heart in this region.

Better results will probably be obtained when certain adjustments have been madé in the technique of injection.

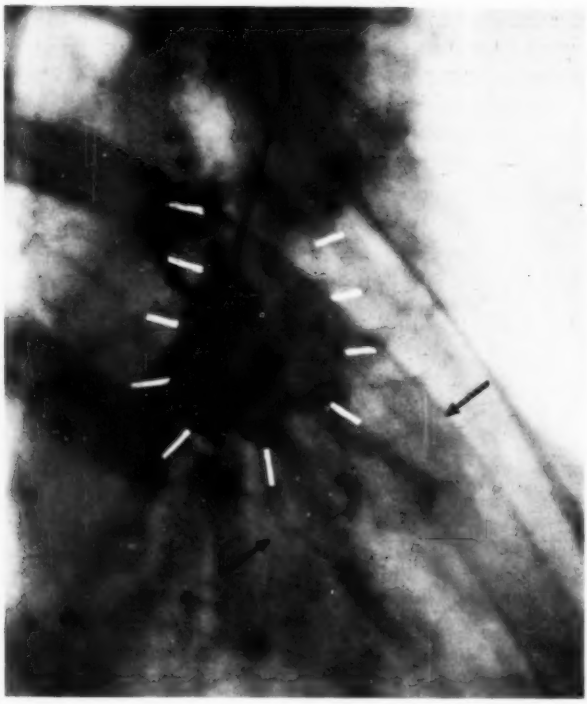

Fig. 2. Attempt at the visualization of coronary arteries in man. Moderate opacification of the bulb of the aorta. The aortic valves are clearly distinguishable. At the normal site of the coronary arteries in the projection concerned — the area between the arrows, caudo-ventral to the bulb — faintly silhouetted vessels, which possibly represent the proximal parts of these arteries, are to be seen.

Complications

Complications arose in 2 cases. In one a moderate degree of mediastinal emphysema developed, owing to the open communication through the cannula between the anterior mediastinum and the outer air. This subsided after a couple of days. The emphysema can be effectively prevented by closing the cannula with a stopcock after the removal of the plunger.

In the other case, extravascular infiltration occurred after perforation of the dorsal wall of the bulb of the aorta and the contrastfluid welled into the pericardium. Exsudative pericarditis developed in this patient, a fact which was verified by roentgenography. Two months after the inter-

vention, however, a control roentgenogram proved that the effusion had been completely absorbed while thorotrast could still be demonstrated in the pericardium, and in the mediastinal lymphatic vessels and lymph glands.

No other complications arose.

Discussion

Owing to this pericarditis complication after the application of thorotrast, attempts to visualize the coronary arteries with this substance were broken off. A disadvantage of thorotrast is that, if it infiltrates extravascularly, it remains for a long time at the site of injection whereas the iodide preparations, used for contrast, are excreted rapidly.[1] The available compounds of the last-mentioned type, however, sometimes cause undesirable vascular reactions which can have deleterious consequences, especially in coronary vessels which are already damaged before the intervention; thorotrast causes no reaction of this kind.

The risk of extravascular infiltration will undoubtedly be reduced as the technique of injection is improved. If no better contrast substance is produced the experiments will be continued with thorotrast along the lines outlined above.

SUMMARY

An important segment of the human circulatory system, the coronary vessels, still remains outside the scope of the angiography. P. Rousthöi has demonstrated in animals that these vessels can be opacified from the bulb of the aorta and the present author has confirmed his observations in the dog. On the basis of these investigations experiments were carried out by the present author with a view to visualizing the coronary vessels in man on the same principle. The technique employed is described. With this method, moderate opacification of the bulb of the aorta was obtained. Faintly silhoutted vessels, which possibly correspond to the proximal parts of the coronary arteries, were to be seen in the area where these vessels are normally situated.

Transient complications occurred in two of the five subjects upon whom aorta puncture and injection of contrast fluid were carried out.

ZUSAMMENFASSUNG

Ein bedeutungsvoller Abschnitt des menschlichen Kreislaufs, die Koronargefässe, ist der Angiographie noch nicht zugängig. P. Rousthöi hat an Tieren gezeigt, dass diese Gefässe vom Bulbus aortae her sichtbar gemacht werden können, und Verf. hat diese Beobachtungen an Hunden bestätigt. Auf der Basis dieser Untersuchungen hat Verf. Versuche angestellt, die bezweckten, die Koronargefässe beim Menschen nach demselben Grundsatz sichtbar zu machen. Die verwendete Technik wird beschrieben. Mit

[1] Another well-known disadvantage of thorotrast is that, even when injected intravascularly, it is for many years retained in the organism.

dieser Methode wurde eine mässig gute Verschattung des Bulbus der Aorta erzielt. Schwach hervortretende Gefässe, die vielleicht den proximalen Partien der Koronargefässe entsprachen, wurden in dem Gebiete sichtbar, wo diese Gefässe normalerweise liegen.

Vorübergehende Komplikationen kamen bei zweien der fünf Fälle vor, an denen Aortapunktion und Injektion von Kontrastflüssigkeit vorgenommen wurde.

RÉSUMÉ

Un segment important du système circulatoire de l'homme, les vaisseaux coronaires, demeure aujourd'hui encore inaccessbile à l'angiographie. P. Rousthöi a démontré chez l'animal, que l'on peut les rendre opaques en opérant du bulbe aortique et l'auteur du présent mémoire a confirmé ses observations en se servant du chien comme matériel d'expérience. Partant de ces expériences il a tenté d'opacifier les vaisseaux coronaires de l'homme en utilisant le même principe. Il décrit la technique utilisée. Il a obtenu, au moyen de ce procédé, une opacité moyenne du bulbe aortique. Une légère silhouette de vaisseaux correspondant à la partie adjacente des vaisseaux coronaires a été notée dans la zône où ces vaisseaux sont situés normalement.

Deux des cinq malades chez lesquels l'auteur a pratiqué la ponction de l'aorte et l'injection de liquide opaque ont présenté des troubles passagers.

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ÜBER DIE MÖGLICHKEITEN DER RÖNTGENTHERAPIE BEI DER BEHANDLUNG DES BRUSTKREBSES[1]

von

S. Mustakallio

Die älteste erfolgreiche und noch immer vorherrschende Methode der Brustkrebsbehandlung ist die Radikaloperation, bei der die ganze Brustdrüse exstirpiert und die Achselhöhle ausgeräumt wird (HALSTED und MEYER 1894).

Nachdem die Röntgentherapie bei der Krebsbehandlung eingeführt worden war, hat man natürlicherweise auch diese Behandlungsweise zur Verbesserung der durch die Radikaloperation erzielten Ergebnisse zu Hilfe genommen. Durch Röntgenbehandlung nach oder vor der Radikaloperation sucht man die bei dieser vielleicht sonst in den Geweben zurückbleibenden Krebszellen zu vernichten. FORSSELL (1928) und BERVEN (1940) betonen ausserdem insbesondere, dass der präoperativen Röntgenbestrahlung auch als Stärkung der antikanzerösen Kräfte grosse Bedeutung zukomme. Dadurch bleibt, wie man hofft, die Patientin wenigstens von örtlichen Karzinomrezidiven verschont. Diese Behandlungsmethode ist denn auch schon seit etwa dreissig Jahre im Gebrauch und wird immer noch allgemein angewandt. Auch scheint sie die Resultate der chirurgischen Behandlung etwas verbessert zu haben, aber eine umfassende und einstimmig anerkannte Verbesserung scheint sie doch nicht zustande gebracht zu haben, denn noch wie vor gibt es namhafte Chirurgen, die ihr so kaum irgend welchen Wert zuerkennen (PACK und LIVINGSTON 1940).

Namentlich in letzter Zeit hat man mehr denn je für die präoperative Behandlung neben der Radikaloperation einzutreten begonnen, während die postoperative oft als unnötig betrachtet wird. So schreibt z. B. KÖHLER (1944): Die kombinierte Vorbestrahlung mit Radikaloperation ist die Methode der Wahl. Dieser Standpunkt wird vor allem damit

[1] Bei der Red. am 27. IV. 1945 eingegangen.

begründet, dass die präoperative Bestrahlung in hohem Masse das Entstehen von Metastasen im Zusammenhang mit der Operation zu verhindern vermag.

Die Behandlungserfolge bei Mammakarzinom haben sich im Laufe der Jahre bedeutend verbessert. Nach den Statistiken des schwedischen *Radiumhemmet* sind dort bei den operierten Fällen in 40 % Heilungen für fünf Jahre erreicht worden (HANSSON 1940, AHLBOM 1941), von diesen gehörten ca. 35 % zum I. und ca. 65 % zum II. Stadium. Bei den Karzinomen im I. Stadium waren Heilungen für fünf Jahre in 71 % und bei denen im II. Stadium in 24 % zu verzeichnen.

PACK und LIVINGSTON polemisieren indes sehr scharf gegen die Notwendigkeit der Röntgentherapie als Ergänzung der Radikaloperation. Sie stützen sich auf grosse chirurgische Statistiken und zeigen, dass man beim Brustkrebs im I. und II. Stadium mit blosser Radikaloperation zu gleich guten Ergebnissen wie mit kombinierter Behandlung kommt. Die von ihnen angeführten Heilungszahlen für fünf Jahre sind folgende: Bei Krebs im I. Stadium (ohne mikroskopisch feststellbare Metastasen in der Axille) beträgt die Nettoheilung 78—80 % und das absolute Heilungssprozent 70—72 %. Entsprechend beläuft sich bei Brustkrebs im II. Stadium (in der Achselhöhle mikroskopisch feststellbare Metastasen) das Heilungsprozent auf nur 22—23 %. Bedient man sich der auf klinische Untersuchung gegründeten Steinthalschen Stadieneinteilung, so ist bei Brustkrebs im II. Stadium (in der Achselhöhle klinisch feststellbare Drüsen) das Heilungsergebnis fast um die Hälfte besser, d. h. 38—42 %. Dieser Unterschied beruht darauf, dass, selbst wenn in der Achselhöhle klinisch palpable Drüsen vorhanden sind, in 32 % dieser Fälle bei der mikroskopischen Untersuchung kein Krebs gefunden wird (HARRINGTON 1935). Nach den genannten Forschern erklärten sich die besseren Ergebnisse mit der kombinierten chirurgisch-röntgenologischen Methode (PFAHLER 1938) daraus, dass die klinische Steinthalsche Einteilung benutzt wurde, während die Chirurgen sich auf einer die mikroskopische Untersuchung der Axillardrüsen gegründeten Einteilung bedienen. Wendet man bei beiden Behandlungsmethoden dieselbe Einteilungsweise an, so sind nach PACK und LIVINGSTON die Ergebnisse der Therapie auch bei den Brustkrebsen im zweiten Stadium gleich. Alle operablen Fälle einberechnet, erreicht man bei beiden Behandlungsweisen 40 % Dauerheilungen.

Die Behandlung des Brustkrebses gründet sich also gegenwärtig hauptsächlich auf die Radikaloperation der Brust und in zweiter Linie auf Röntgentherapie. Ist nun die Radikaloperation eine ideale Therapie? Diese Frage ist zu verneinen. Die Exstirpation der ganzen Brust und der Brustmuskeln ist eine verstümmelnde Operation. Besonders auf junge Frauen übt sie ausserdem einen psychisch schädigenden Einfluss aus.

Desgleichen darf der Nachteil, der durch Elephantiasis einer Oberextremität entsteht, nicht unterschätzt werden. Diese tritt in 15—20 % der operierten Fälle ein und bleibt in etwa 10 % permanent (BEHAN 1938). Ausserdem wird die Hand in vielen Fällen träge. Das bedeutet für die Patientin ein grosses Hindernis und vermindert oft in hohem Masse ihre Arbeitsfähigkeit. So teilt KALIMA (1928) über sein Material mit, dass von 74 Patientinnen nur 51 nach der Operation derselben Beschäftigung nachgingen wie vorher, dass aber die Energie der Oberextremität bei 23 Patientinnen dauernd herabgesetzt war, so dass sie ihre gewöhnliche Arbeit einschränken oder fremde Hilfe in Anspruch nehmen mussten. Zu einem annähernd gleichen Ergebnis ist diesbezüglich O.PIKKARAINEN (1930) in seiner Statistik gelangt. Von 170 Patientinnen hatten nur 66, d. h. 39 %, von der Operation keine Nachteile. In 24 Fällen (14 %) war die Arbeitskraft vollständig verlorengegangen. Die gegenwärtige Behandlungsweise kann also an sich nicht als eine ideale gelten, die nicht verbessert zu werden brauchte. Die Radikaloperation des Brustkrebses ist indes eine schon alte und hochentwickelte Behandlungsmethode, so dass auf dieser Linie kaum eine bemerkenswerte Verbesserung in der Behandlung des Brustkrebses zu erwarten ist. Dagegen schliesst die Strahlentherapie offenbar noch ungenutzte Möglichkeiten ein. In der vorliegenden Untersuchung soll denn auch geprüft werden, ob man vielleicht auf Grund des Materials des von mir geleiteten Krankenhauses zu einfacheren und für die Patientin schonenderen Behandlungsverfahren gelangen kann.

Das Material

Im Zentralinstitut für Strahlentherapie in Finnland wurden in den Jahren 1936—1943 insgesamt 384 Brustkrebskranke behandelt. Die meisten dieser Fälle sind von verschiedenen Chirurgen operiert und aus verschiedenen Gegenden Finnlands zur Röntgenbestrahlung eingeliefert worden. Aus diesem Grunde kann ich auch das von mir besprochene Material nicht nach STEINTHAL, BRODERS oder auf Grund mikroskopischer Untersuchung der Axillardrüsen in die üblichen Brustkrebsstadien einteilen, denn die Chirurgen, die dem Zentralinstitut Patientinnen zuwiesen, haben oft nicht angegeben, welchem Stadium der operierte Krebs angehörte. Nur ein kleiner Teil der Fälle hat präoperative Röntgenbestrahlung erhalten, daher werden auch sie nicht in einer gesonderten Gruppe behandelt. Verhältnismässig viele Patientinnen sind wegen Metastasen oder als inoperabel zur Behandlung eingesandt worden.

Einer Anstalt für Strahlentherapie bietet meines Erachtens das Entwicklungsstadium der durch klinische Untersuchung feststellbaren Krebserkrankung bei der Aufnahme der Patientinnen in das Krankenhaus

eine richtige Einteilungsgrundlage. Nach dieser Einteilungsweise zerfällt mein Material folgendermassen in verschiedene Gruppen:

Radikaloperierte, ohne feststellbare Metastasen zur Röntgenbehandlung gekommen	166
Radikaloperierte mit feststellbaren Metastasen bei Beginn der Röntgenbestrahlung	103
Durch Tumorexstirpation behandelte Fälle	23
Inoperable Fälle	92
	384

Da die Röntgenbestrahlung einen guten palliativen Einfluss auf die Metastasen und die inoperablen Fälle ausübt, sind auch sie einer Behandlung unterzogen worden, soweit der Allgemeinzustand der Patientinnen es gestattet hat. So sind nur die Fälle mit ganz schlechtem Allgemeinstatus, die dem Tode nahen, ohne Behandlung geblieben. Auch Lungenmetastasefälle haben in gewissem Masse Strahlenbehandlung bekommen, und oft ist festgetellt worden, dass die Patientinnen beträchtlichen Nutzen davon gehabt haben.

Die Röntgentherapie

Die Art und die Menge der Röntgenbehandlung sind in hohem Grade von der Beschaffenheit der Fälle anhängig gewesen. Am häufigsten wurde postoperative Röntgentherapie benutzt, da die Chirurgen daran gewöhnt sind und ihre Patientinnen noch nicht zu präoperativer Bestrahlung anweisen. Persönlich möchte ich jedoch präoperative Behandlung empfehlen. Als *postoperative Behandlung* wurden auf die Brustwand, das Operationsfeld, meistens 1,500—2,000 r, auf der Haut gemessen, gegeben. Die Einzeldosis betrug 300 r. Ausserdem wurden 1,000—1,750 r in die Achselhöhle gegeben und als drittes Feld diente die Gegend der Schlüsselbeingruben, auf die 2,100—2,500 r appliziert wurden. Bei den beiden letzteren Stellen umfasste die Einzeldosis 350 r. Bei allen Behandlungen wurde als Filter 0.5 mm Cu + 1 Al benutzt, die übrigen Werte waren kV 180, mA 4, Abstand 40 cm. Das Feld war im Operationsgebiet offen, in der Achselgrube 10 × 15 cm und in der Schlüsselbeingrube 8 × 10 cm. Die Behandlungen wurden einmal täglich, nur nicht an Sonn- und Feiertagen, gegeben. Die Kur wurde nicht erneuert, wenn keine Metastasen erschienen. Als *präoperative* Röntgentherapie wurden auf die Brust selbst durch zwei entgegengesetzte Seitenfelder insgesamt 2,500—3,000 r verabfolgt. Wenn in der Achselhöhle auch nur wenig Drüsen zu palpieren waren, wurden auch auf sie 1,500 r appliziert, desgleichen, wenn nötig, in die Schlüsselbeingrube. Kam ausserdem postoperative Bestrahlung zur Anwendung, so wurde das Brustgebiet nicht mehr behandelt, sondern die Therapie nur auf die Achselhöhle und die Schlüsselbeingrube gerichtet.

Bei der *Behandlung der Metastasen* wurde, soweit möglich, nach radikaler Röntgenbehandlung gestrebt. Dabei wurden also grosse Dosen benutzt, soweit es sich nicht von Anfang an nur um eine symptomatische Bestrahlung handelte.

Als Beispiel sei eine 35jährige Frau angeführt, bei der eine Radikaloperation ausgeführt worden war und die am 19. 6. 1939 in Röntgenbehandlung kam. Als sie aufgenommen wurde, hatte sie eine grosse Metastasenverhärtung in der Achselhöhle. Auf diese bekam sie auf drei Felder folgende Mengen: von vorn 3,150 r, von hinten 2,800 r und direkt in die Achselhöhle 2,450 r, zusammen 8,400 r. Fünf Monate später erhielt sie in dieselbe Achselhöhle noch 6,000 r, da die Metastase anscheinend zu wachsen begann. Nach anderthalb Jahren wurde die Patientin aus demselben Grunde wieder behandelt, sie bekam 2,450 r. Danach war sie symptomlos und lebt nun schon fünf Jahre, ohne dass sich an der Metastasenstelle etwas zeigte, was auf ein Rezidiv hinwiese. Diese Patientin bekam also in dieselbe Achselhöhle durch verschiedene Felder insgesamt 16,850 r, auf der Haut gemessen.

Mit *blosser Exstirpation und Röntgen* wurden 23 Brustkrebsfälle behandelt. In allen diesen Fällen blieb also ein grosser Teil der Brust erhalten, auch wurde keine Evakuation der Achselhöhle vorgenommen. Eine histologische Bestätigung der Diagnose liegt in 22 der Fälle vor; bei einem vor mehr als drei Jahren behandelten Fall, der eine sehr starke präoperative Bestrahlung erhielt, ist die histologische Diagnose etwas unsicher. Diese Fälle wurden etwas verschieden mit Röntgenstrahlen behandelt, da sie teils in anderen Krankenhäusern, teils im Zentralinstitut für Strahlentherapie operiert worden waren. War die Operation primär ausgeführt worden, so wurde meist sehr starke Nachbehandlung gegeben.

Bei *inoperablen Karzinomen* wurde eine möglichst grosse Dosis verabfolgt. In diesen Fällen verhindern jedoch die Fernmetastasen die Heilung der Patientinnen. Die Behandlung hat jahrelang gedauert.

Behandlungsergebnisse

Die Ergebnisse der Therapie werden aus den Tabellen 1—6 ersichtlich.

In den Fällen, die nach der Operation zur Röntgenbehandlung kamen, ohne dass klinisch Metastasen festgestellt werden konnten, waren die Resultate ausgezeichnet. In den letzten Jahren haben sich die Resultate deutlich verschlechtert. Dies dürfte darauf beruhen, dass infolge des durch den Krieg hervorgerufenen Mangels an Arbeitskräften nicht alle Patientinnen zu Beginn der Behandlung so sorgfältig wie in Friedenszeiten untersucht werden konnten. Jedenfalls zeigen die Ergebnisse, dass die Fälle, in denen etwa vier Wochen nach der Operation keine erkennbaren Metastasen zu palpieren sind, eine gute Prognose haben. Metastasen erscheinen besonders in den Supraklavikulargruben oft sehr bald nach der Operation.

Häufig ist es denn auch vorgekommen, dass bei den zu postoperativer Behandlung kommenden Patientinnen schon in der Supraklavikulargrube oder anderswo Metastasen festgestellt wurden. In den meisten Fällen können die oberflächlichen Metastasen durch Röntgenbehandlung beherrscht und sehr oft zu völligem Verschwinden gebracht werden. Doch ist in den Fällen, in denen schon bei Beginn der Röntgenbehandlung Metastasen festgestellt wurden, die Prognose ausserordentlich schlecht.

Alle radikaloperierten Brustkrebse in Betracht gezogen, ist das Ergebnis der Behandlung ein verhältnismässig schlechtes. Nach fünf Jahren sind nur noch 38 % dieser Patientinnen am Leben. Dabei ist jedoch zu beachten, dass von diesen vor mindestens fünf Jahren behandelten Fällen, insgesamt 79, 48 im Rezidivstadium in Behandlung gekommen sind. Dadurch wird natürlich das Behandlungsresultat verschlechtert.

Tabelle 1

Die radikaloperierten Krebspatientinnen, die ohne feststellbare Metastasen zur Röntgenbehandlung gekommen sind. Durchschnittliches Alter 50 Jahre.

Es lebten symptomfrei wenigstens					
1 Jahr	140	von	166	Patientinnen	= 85 %
2 Jahre	88	»	124	»	= 71 %
3 »	56	»	75	»	= 75 %
4 »	37	»	47	»	= 79 %
5 »	25	»	31	»	= 80 %

Tabelle 2

Die radikaloperierten Krebspatientinnen, die bei Beginn der Röntgenbehandlung feststellbare Metastasen aufwiesen. Durchschnittliches Alter 51.8 Jahre.

Es leben					
1 Jahr	51	von	103	Patientinnen	= 49 %
2 Jahre	30	»	89	»	= 34 %
3 »	15	»	74	»	= 20 %
4 »	12	»	58	»	= 20 %
5 »	5	»	48	»	= 10 %

Tabelle 3

Alle radikaloperierten, mit Röntgen behandelten Brustkrebse.

Es lebten symptomfrei wenigstens					
1 Jahr	191	von	269	Patientinnen	= 71 %
2 Jahre	118	»	213	»	= 55 %
3 »	71	»	149	»	= 48 %
4 »	49	»	105	»	= 47 %
5 »	30	»	79	»	= 38 %

Nur mit Tumorexstirpation und Röntgen behandelte Fälle

Tabelle 4

Mit Tumorexstirpation behandelte Brustkrebse. Durchschnittliches Alter 57.4 Jahre. Ein Todesfall.

Es leben symptomfrei

1 Jahr	23	von	23	Patientinnen
2 Jahre	16	»	17	»
3 »	12	»	13	»
4 »	11	»	12	»
5 »	5	»	6	»

Eine Patientin starb symptomfrei an Herzkrankheit.

Die Ergebnisse in dieser Gruppe sind ausserordentlich gut, denn *bisher ist keine einzige dieser Patientinnen an Krebs gestorben.* Der einzige Exitus, der vorgekommen ist, ist auf das Konto einer Herzkrankheit zu setzen. Sie hatte schon bei der Einleitung der Therapie einen sehr schweren Herzfehler und war daher die ganze Zeit in ärztlicher Behandlung. Eine Radikaloperation kam daher nicht in Frage. Als die Patientin etwa 1 Jahr 10 Mon. nach Beginn der Behandlung starb, waren bei ihr keinerlei Anzeichen von Rezidiven oder Metastasen festzustellen.

Das vorzügliche Ergebnis bei dieser Gruppe beruht natürlich in erster Linie darauf, dass diese Fälle meist schon zu Beginn der Behandlung »gute Fälle» waren, d. h. zum ersten Stadium gehörten. Diese nur mit Tumorexstirpation und Röntgentherapie behandelten Fälle zeigen deutlich, dass man bei beginnenden Brustkrebsfällen mit dieser konservativen Behandlungsweise zu sehr guten Ergebnissen gelangen kann. Da die hier in Frage stehenden Fälle meines Erachtens wichtig und interessant sind, sei über diejenigen berichtet, die wenigstens drei Jahre beobachtet worden sind. Tabelle 5.

Wie man aus der Tabelle ersieht, schwankten die Dimensionen der Geschwulst zwischen Faustgrösse und einem nicht mit den Fingern palpablen kleinen Tumor. Acht von diesen 13 Patientinnen hatten eine intensive präoperative Röntgenbehandlung bekommen und einige von den Geschwülsten waren viel kleiner geworden. In einem Fall waren alle lebenden Karzinomzellen verschwunden. Die präoperative Röntgentherapie hat wahrscheinlich eine wichtige Bedeutung für das Gelingen der ganzen Behandlung. Vermutlich wird die Metastasierungsgefahr dadurch kleiner, und es ist auch möglich, dass die antikanzerösen Kräfte des Körpers durch die präoperative Röntgenbehandlung verstärkt werden. Darum wäre es wichtig, immer eine intensive präoperative Röntgenbestrahlung vor der Exstirpation des Tumors zu geben. Im letzten Fall wurde neben dem Sternum eine Metastase festgestellt, die durch

Tabelle

Brustkrebsfälle, die durch Exstirpation des Tumors und Röntgen

Nr.	Alter	Aufnahme	Anamnese	Status localis	Operation
73/37	67	13. 1. 1937	Vor 3 Wochen bemerkte Pat. einen kleinen Knoten im oberen Teil der rechten Brust. Sie war wegen eines Herzfehlers vom September 1936 an bettlägerig gewesen.	Ein im Durchmesser etwa 2 cm grosser, beweglicher Tumor in der rechten Brust im oberen medialen Quadranten. Im Herzen Vorhofflimmern.	6. 2. 1937. Exstirpation mit dem Diathermiemesser.
329/37	64	15. 3. 1937	»Blutende Mamma» seit 3 Jahren. Während derselben Zeit ein Tumor in der Brust. Will sich keiner Operation unterwerfen.	In der rechten Brust ein faustgrosser, beweglicher Knoten unterhalb der Mamille. In der Axille eine bewegliche Drüse von ca. 2 cm im Durchmesser.	Resttumor exstirpiert am 7. 10. 1940. Axillenmetastase nicht exstirpiert.
528/37	45	12. 5. 1937	2 Jahre lang »blutende Mamma»	Deutlicher Tumor, nicht schmerzhaft. In der Achselhöhle keine Drüsen.	Exstirpatio tumoris
936/38	48	7. 7. 1938	Im Herbst 1937 bemerkte Pat. einen Knoten in der rechten Brust. Die Mamille zog sich allmählich einwärts. Einige Monate Schmerzen in der Brust.	Mitten in der rechten Brust ein etwa $3^1/_2$ cm im Durchmesser haltender platter Tumor, der auf seiner Unterlage beweglich ist, aber die Mamille ist an ihm fixiert. In der Achselhöhle keine Drüsen.	28. 8. 1938. Exstirpatio tumoris, im Durchmesser $2^1/_4$ cm. 28. 3. 1939. Evacuatio axillae. In der Achselhöhle eine Drüse von der Grösse einer kleinen Pflaume. Die Brust bleibt erhalten.
528/39	33	24. 2. 1939	3 Wochen vor der Aufnahme in das Krankenhaus war primär ein Tumor exstirpiert worden, der sich als daumenendgross erwies und am Aussenrand der Brust lateral von der Mamilla lag.	Operationsnarbe, kein Tumor, in der Achselhöhle keine Drüsen.	Exstirpatio tumoris, s. Anamnese.
674/39	65	14. 3. 1939	1936 wurde Brustkrebs konstatiert, doch lehnte Pat. Behandlung ab.	In der rechten Brust lateralwärts von der Areola ein fast faustgrosser, an der Haut festsitzender Tumor mit roter Oberfläche, der auf seiner Unterlage beweglich ist. In der Achselhöhle keine Drüsen.	11. 9. 1939. Exstirpatio tumoris. Der auf Hühnereigrösse verkleinerte Tumor wird entfernt.

5

behandelt und danach wenigstens drei Jahre beobachtet worden sind.

Histologische Diagnose	Röntgentherapie	Ergebnis
Sehr atypische Krebszellen im Bindegewebe.	*Präoperative Behandlung.* 13. 1.—23. 1. 1937 auf die Brust 1,900 r. *Postoperative Behandlung.* 12 Tage nach der Operation. 18. 2.—22. 2. Gegend der Klavikula 600 r. 23. 2.—25. 2. Achselhöhle 600 r. 26. 2.—1. 5. Brust 600 r. 20. 5.—31. 5. Brust 750 r. Gegend der Klavikula 900 r. 26. 7.—3. 8. 1937 linke Klavikularregion 1,900 r.	Durch die Röntgentherapie hatte sich der Tumor gegen den Zustand vor der Operation auf ungefähr die Hälfte verkleinert. Pat. hat Erysipelas bekommen und ist an Herzschwäche im Oktober 1938 gestorben. Von Karzinom waren keine Zeichen zu finden.
11. 11. 1937. Carcinoma colloides. Bindegewebe hyalinisiert. Zwischen den Fibrillen reichlich Schleim. Karzinomzellen ziemlich zahlreich. Ihre Atypie gross. 21. 8. 1939 gleicher Befund. 7. 5. 1940 nur noch stellenweise erhaltene Karzinomzellenmassen. Atypie immer noch gross.	(1935 bekam Pat. in der Chirurgischen Klinik zu Helsinki im August 100 % HED auf die Brust und 100 % in die Axille, im September 125 % auf die Brust und 125 % in die Axille. Im August 1936 auf die Brust 200 %. Der Tumor blieb unverändert.) 15. 3.—25. 3. 1937 auf die Brust 1,200 r, in die Axille 1,500 r. 19. 11. 1937 Intubation der Radiumnadel in den Brusttumor: 15 × 10 mgr-Radiumnadeln 4 Std. 11. 4.- 14. 4. 1938 Röntgentherapie auf die Brust 1,400 r. 1. 6.—10. 6. 1938 Röntgentherapie in die Axille 2,800 r. 21. 1. —3. 2. 1941 in die Axille 3,200 r.	Durch die Röntgentherapie verkleinerte sich der Tumor auf etwa Hühnereigrösse. Die Axillenmetastase verschwand. Pat. völlig arbeitsfähig gewesen. Die Haut hatte nicht erheblich gelitten. Am 26. 10. 1944 symptomfrei und arbeitsfähig.
Karzinom nur in einem kleinen Gebiet.	*Postoperative Behandlung.* 12. 5.—31. 5. 1937 auf die Brust 1,000 r, in die Axille 1,000 r, in die Klavikularregion 2,000 r.	2. 12. 1943. Symptomfrei und arbeitsfähig.
28. 8. 1938. Adenokarzinom. Die Karzinomzellen in kompaktem Bindegewebe. Die Grösse der Kerne variiert beträchtlich. 28. 3. 1939 Metastase: Eine Lymphdrüse, die Massen von Karzinomzellen enthält.	*Präoperative Behandlung.* 7. 7.—22. 7. 1938 auf die Brust 4,400 r von zwei entgegengesetzten Feldern aus. 23. 8. —29. 8. in die Axille 1,600 r. 30. 8. —7. 9. in die Schlüsselbeingruben 2,000 r. 5. 9.—13. 9. auf die Brust 1,150 r, 17. 4.—5. 5. 1939 in die Axille von zwei Feldern aus zusammen 5,600 r, 6. 5.—12. 5. auf eine in der Fossa supraclavicularis palpable Drüse 3,000 r.	Durch die präoperative Behandlung verkleinerte sich der Tumor um etwa ein Drittel. Pat. ist völlig arbeitsfähig gewesen. Im Gebiet der Bestrahlungsfelder etwas Teleangiektasien. Am 28. 11. 1944 symptomfrei und arbeitsfähig.
Adenokarzinom.	*Postoperative Behandlung.* 24. 2.—11. 3. 1939 auf die Brust von zwei entgegengesetzten Feldern aus zusammen 4,900 r. 13. 3.—18. 3. in die Schlüsselbeingruben 1,750 r, 20. 3.—21. 3. 1939 in die Axille 700 r.	22. 11. 1944. Symptomfrei und arbeitsfähig.
Im Bindegewebe hyalinisierte, scharf begrenzte Partien, an deren Stelle augenscheinlich die Karzinomgebiete gelegen haben.	*Präoperative Behandlung.* 16. 3.—6. 4. 1939 auf die Brust von 3 Feldern aus 6,400 r, 18. 4.—19. 4. 1939 in die Gegend der Klavikulargruben 500 r.	Durch die präoperative Behandlung verkleinerte sich der Tumor von Faust- bis Hühnereigrösse. 22. 11. 1944. Symptomfrei und arbeitsfähig.

Tabelle

Nr.	Alter	Aufnahme	Anamnese	Status localis	Operation
965/40	65	31. 7. 1940	Im November 1939 bemerkte Pat. in der linken Brust einen Knoten.	Das Karzinom lag im medialen oberen Quadranten. In der Achselhöhle einige bohnengrosse Drüsen.	15. 7. 1940. Exstirpatio tumoris.
1179/39	44	3. 9. 1940	Pat. hat am unteren Ende des rechten Femur ein Osteosarkom gehabt. Amputation am 18. 5. 1936, danach symptomlos. Mitte August bemerkte sie einen kleinen Knoten in der rechten Brust.	Im oberen lateralen Segment der rechten Brust ein beweglicher Knoten von ca 2 cm im Durchmesser. In der Axille keine Drüsen.	5. 9. 1940. Exstirpatio tumoris. Ein pflaumengrosser, fester Tumor, der mit seiner Umgebung verwachsen ist.
1212/40	44	13. 9. 1940	Etwa 1½ Monate fand Pat. in der rechten Brust einen kleinen Knoten.	Im medialen oberen Quadranten der rechten Mamma ein pflaumengrosser Knoten, der auf seiner Unterlage und gegen die Haut beweglich ist. In der Axille keine Drüsen.	21. 1. 1941. Exstirpatio tumoris. Der Tumor makroskopisch verschwunden.
1669/40	56	10. 12. 1940	Vor 8½ Wochen wurde ein Karzinom in der linken Brust operiert. 3 Monate beobachtete Pat. einen Knoten in der rechten Brust. Will sich nicht operieren lassen.	In der rechten Brust direkt über der Areola eine Verhärtung von ca. 3 cm im Durchmesser. An der Mamille fixiert. In der Axille keine Drüsen.	4. 1. 1941. Exstirpatio tumoris.
401/41	44	30. 1. 1941	Pat. bemerkte 1 Monat in der rechten Brust einen hühnereigrossen Knoten.	Ein hühnereigrosser, beweglicher Tumor oberhalb der Areola. In der Axille keine Drüsen.	8. 1. 1941. Exstirpatio tumoris.
496/41	58	7. 2. 1941	Vor 3 Jahren stellte Pat. am oberen Rand der linken Brust einen Knoten fest, der bald darauf exstirpiert wurde. War alsdann symptomlos gewesen, bis sie vor 2 Tagen einen Knoten in der linken Achselhöhle bemerkte.	Linke Brust etwas kleiner als die rechte, darin kein Knoten. In der linken Axille eine harte und bewegliche Drüse von ca. 2 cm Durchmesser.	24. 10. 1941. Exstirpatio tumoris. Der Tumor hat einen Durchmesser von etwa 1½ cm. Der Resttumor wird entfernt.
519/41	50	10. 2. 1941	Vor etwa 4 Monaten bemerkte Pat. einen pflaumengrossen Knoten im oberen äusseren Quadranten der linken Brust. Am 14. 1. 1941 wurde der Knoten in einem Kommunalkrankenhaus exstirpiert.	Im oberen äusseren Quadranten der linken Mamma eine 3 cm lange Operationsnarbe mit infiltrierter Umgebung. Im oberen Teil der Brust über der Areola ebenfalls Knoten.	14. 1. 1941. Unvollständige Exstirpation.

5 (Forts.)

Histologische Diagnose	Röntgentherapie	Ergebnis
Teils papilläres, teils solides Karzinom.	*Postoperative Behandlung.* 31. 7.—22. 8. 1940 auf die Brust von zwei Feldern aus zusammen 3,000 r, in die Axille 1,500 r, in die Schlüsselbeingegend 2,000 r.	5. 6. 1945. Symptomfrei und arbeitsfähig.
Adenokarzinom.	*Postoperative Behandlung.* 11. 9.—16. 9. 1940 in die Klavikulargrube 1,000 r, in die Axille 1,050 r, 18. 9.—2. 10. 1940 auf die Brust von drei Feldern aus zusammen 4,550 r.	17. 11. 1944. Symptomfrei und arbeitsfähig.
Carcinoma solidum. Inmitten des hyalinisierten Bindegewebes atypische Carcinoma solidum-Massen.	*Präoperative Behandlung.* 13. 9.—26. 9. 1940 auf die Brust von zwei Feldern aus 4,800 r, 11. 2.—25. 2. in die Axille 2,800 r, in die Klavikularregion 1,750 r.	7. 1. 1944. Symptomfrei und arbeitsfähig.
Adenokarzinom. Manche Karzinomzellen degeneriert. In der Brust auch Mastopathia cystica.	*Präoperative Behandlung.* 10. 12.—18. 12. 1940 auf die Brust von zwei Feldern aus zusammen 3,200 r. *Postoperative Behandlung* 13. 2.—5. 2. 1941 in die Axille 1,200 r, 6. 2.—14. 2. auf die Brust 3,200 r, 18. 2.—25. 2. 1941 in die Klavikularregion 2,800 r.	29. 6. 1945. Symptomfrei und arbeitsfähig.
Karzinomzellen in kleinen Inseln im Bindegewebe.	*Präoperative Behandlung.* 10. 8.—20. 8. 1940 auf die Brust 2,000 r. *Postoperative Behandlung:* 30. 1.—20. 2. 1941 auf die Brust 2,100 r, in die Axille 2,000 r, in die Klavikularregion 2,100 r.	7. 6. 1944. Symptomfrei und arbeitsfähig.
24. 10. 1941. Karzinom. 9. 1. 1942 kein Karzinom in der Probe.	8. 2. —24. 2. 1941 in die Axille von zwei Feldern aus zusammen 5,300 r. *Präoperative Behandlung.* 12. 9.—17. 9. 1941 direkt in die linke Axille 2,000 r, 21. 1.—29. 1. 1942 in die linke Axille 3,200 r.	12. 1. 1945. Symptomfrei und arbeitsfähig.
Solide Geschwulstmassen im Bindegewebe und in den Lymphgefässen. Carcinoma solidum.	*Postoperative Behandlung:* 10. 2.—7. 3. 1941 auf die Brust 6,400 r. von zwei Feldern aus, oberhalb der Brust 3,200 r, in die Axille 3,200 r.	Gehört eigentlich nicht zu diesem Material, da Pat. schon zu Beginn der Behandlung in der Mamma zahlreiche Karzinomknoten hatte, die nicht exstirpiert wurden. Sie verschwanden durch Röntgentherapie. Am 14. 8. 1944 wurde auf der linken Seite neben dem Sternum eine Metastase festgestellt. Auf diese wurden von zwei Feldern aus zusammen 4,900 r gegeben. Die Metastase verschwand gänzlich.

Röntgentherapie verschwand. Dieser Fall lässt sich nicht mit den anderen Fällen auf eine Stufe stellen, da das in der Brust vorhandene Karzinom bei der Operation nicht ganz exstirpiert wurde, sondern in der Brust zu Beginn der Behandlung mehrere Krebsknoten zu konstatieren waren.

Es versteht sich von selbst, dass Metastasen zu einem gewissen Prozentsatz auch in beginnenden, mit Tumorexstirpation und Röntgen behandelten Fällen von Brustkrebs vorkommen werden. Bisher scheint es jedoch, als werde das Metastasenprozent zum wenigsten nicht grösser als in den radikaloperierten Fällen sein.

Tabelle 6

Die inoperablen, mit Röntgen behandelten Brustkrebse. Durschnittliches Alter 58.7 Jahre. Am Leben 26 Patientinnen, gestorben 66.

	Am Leben	Symptomfrei		
1 Jahr.....	39	15	Patientinnen von 92	16 %
2 Jahre	15	11	» » 72	15 %
3 »	11	8	» » 56	14 %
4 »	4	4	» » 36	11 %
5 »	2	2	» » 25	8 %

Die Tabelle der inoperablen Brustkrebse zeigt, dass die Behandlungsergebnisse quoad vitam auch in diesen Fällen sehr schlecht sind. Dagegen ist das symptomatische Resultat der Behandlung in den meisten Fällen vorzüglich, und dadurch ist die Röntgentherapie in diesen Fällen die Methode der Wahl. Ausserdem ist zu betonen, dass auch in diesen inoperablen Karzinomfällen einige noch nach 3—5 Jahren symptomfrei sind. Dieses Resultat zeigt, dass durch Röntgentherapie auch weitgekommene Krebsgeschwülste verschwunden sind. Das bedeutet, dass durch Röntgenbehandlung Widerstandsfähigkeit des Körpers entgegen den mit grosser Wahrscheinlichkeit vorhandenen Fernmetastasen soviel zugenommen hat, dass die jahrelange Symptomfreiheit erreicht worden ist. Diese Tatsache stützt die von mir früher erwähnte Meinung von FORSSELL und BERVEN, dass der präoperativen Röntgenbestrahlung auch als Stärkung der antikanzerösen Kräfte grosse Bedeutung zukomme.

Als Beispiel sei eine 52jährige Frau angeführt, die in der linken Brust Krebs und unter der Brust vorn eine in der Brustwand festsitzende fast faustgrosse Metastase hatte. Eine histologische Bestätigung zeigt Carcinoma colloides. Die Patientin kam am 31. 1. 1937 zur Behandlung. Anfangs erhielt sie auf die Brust 3,500 r und auf die Metastase 3,000 r in Einzeldosen von 350 r. Zwei Monate später erhielt sie weiter auf die Brust 1,200 r und auf die Metastase 3,000 r, und nachdem noch vier Monate vergangen waren, empfing sie ferner auf die Metastase 2,700 r. Danach ist die Patientin symptomfrei gewesen, und von dem Tumor ist keine Spur zu erkennen. Bei den meisten anderen Fällen sind weit grössere Röntgendosen erteilt worden.

Die Todesursache

Es ist von Interesse nachzusehen, welche in diesen verschiedenen Brustkrebsgruppen die hauptsächliche Todesursache gewesen ist. Leider sind nur in ganz wenigen Fällen Obduktionen ausgeführt worden, denn die Patientinnen sind meistens zu Hause gestorben. Da die Patientinnen aber von Beginn der Behandlung an während der ganzen Zeit verfolgt worden sind, konnte in zahlreichen Fällen wenigstens festgestellt werden, an welchen Stellen der Krebs beim Tode der Patientinnen so weit vorgeschritten war, dass er als die nächste Todesursache zu betrachten ist. Die eigentliche Todesursache ist in den meisten Fällen natürlich die gesamte Krebskrankheit mit ihren zahlreichen im ganzen Körper disseminierten Metastasen. Diese für die klinische Untersuchung oft unsichtbaren Metastasen können schon an sich die Todesursache bilden, aber in den meisten Fällen kann doch eine Metastase die Oberhand gewonnen und alle anderen in den Schatten gestellt haben.

Tabelle 7

Tabelle über die Todesursache bei Brustkrebs. Aus der Zusammenstellung werden die Behandlungsmassnahmen ausser der Röntgenbestrahlung wie auch das eventuelle Vorhandensein von Metastasen zu Beginn der Röntgenbestrahlung ersichtlich.

Stelle der Metastase, die den Tod bedingt hat	Rad.-Op. keine Metast.	Rad.-Op. und Metast.	Nur Exstirp. der Ca	Inoperable Ca	Insgesamt
Lungen, Pleura Mediastinum..	16	26	—	12	54
Allgemeine Karzinose	4	25	—	8	37
Knochensystem	5	10	—	6	21
Gehirn	2	5	—	1	8
Leber	2	1	—	3	6
Bauchhöhle	—	4	—	2	6
Primäres Ca, Achselhöhle und Hals.....	—	1	—	5	6
Angaben fehlen	11	12	—	24	47
Keine Metastasen, interkurrent gestorben	3	—	1	5	9
Gestorben insgesamt	43	84	1	66	194

In der Tabelle 7 über die Todesursache sind nur die Fälle berücksichtigt, in denen diese ziemlich bekannt war. Die Patientin ist jeweils in die Gruppe der Todesursache eingereiht, die deutlich vorherrschend gewesen ist. In manchen Fällen konnten beim Tode der Patientinnen auch an anderen als an der vorherrschenden Stelle Metastasen festgestellt werden.

Wie aus der Tabelle ersichtlich, sind die Lungenmetastasen in allen Brustkrebsgruppen unbedingt die häufigste Todesursache; sie machen

39 % aller Fälle aus. Auch ist die allgemeine Karzinose sehr gewöhnlich. Sie ist in der Tat wahrscheinlich die allerhäufigste Todesursache, obgleich die Lungenmetastasen in Fällen von Exitus oft in dem klinischen Bild dominieren. In den Fällen, wo örtliche, Achselhöhlen-, Schlüsselbeingruben- oder Halsmetastasen auftraten, konnten diese, mit einigen Ausnahmen, von vornherein durch Röntgentherapie beherrscht und geheilt werden.

Die Brustkrebspatientinnen starben also fast ausnahmslos an Fernmetastasen. Von 194 zum Exitus gegangenen Patientinnen sind nur 6 an örtlichem Krebs verschieden. Für die Entwicklung der Brustkrebstherapie wäre es natürlich wichtig zu wissen, in welchem Stadium die Fernmetastasen enstehen. Das vorgeführte Material gibt Gelegenheit, diese Frage näher zu betrachten.

Es ist klar, dass die Fernmetastasen sich entweder vor der Operation oder während derselben in Bewegung gesetzt haben und entweder direkt von dem primären Brustkrebs oder von Lymphknoten- oder sonstigen Metastasen abstammen. Über diese Frage gibt meines Erachtens weiteren Aufschluss die Verfolgung der Fälle, die Röntgenbestrahlung unterworfen worden sind bevor sie klinisch feststellbare Metastasen aufgewiesen haben. In Tabelle 8 stelle ich alle derartigen Fälle zusammen, die vom Beginn der Behandlung bis zum Tode verfolgt worden sind. Die Fälle, in denen bei der Einleitung der Therapie schon nachweisbare Metastasen vorgelegen haben, sind hier also nicht berücksichtigt worden, denn bei manchen dieser Fälle können durch Vermittlung örtlicher Metastasen Fernmetastasen entstanden sein.

Wie aus Tabelle 8 ersichtlich, haben sich die Metastasen in keinem der Fälle nach der Operation durch erkennbare Metastasen der Operationsgegend oder der Schlüsselbeingruben ausgebreitet. Es ist denn auch durchaus einleuchtend, dass die Krebszellen auf einem anderen Wege nach den Metastasestellen verschleppt worden sind. Als Wanderweg kommen die unmittelbar zu den Lymphknoten des Mediastinums führenden Lymphgefässe in Betracht. Eine mit dem Blut vor sich gegangene embolische Metastasierung ist natürlich auch gut möglich. Dagegen hat die Strahlenbehandlung das Auftreten von örtlichen Metastasen offenbar verhindert. In einem grossen Teil der Fälle, die allerdings erst zur Röntgenbehandlung gekommen sind, wenn bereits Lymphknotenmetastasen in der Achselhöhle oder in der Schlüsselbeingrube haben festgestellt werden können, scheint die Sachlage doch dieselbe wie bei der eben genannten Gruppe zu sein. Ein beträchtlicher Teil der Patientinnen war wegen Fernmetastasen in Behandlung gekommen, ohne dass örtliche Metastasen zu konstatieren waren. Auch in den Fällen, wo zu Beginn der Behandlung örtliche Metastasen vorhanden gewesen sind, zeigen die oft weitentwickelten Fernmetastasen, dass die Krebszellen sich zuerst an den Stellen der

Tabelle 8

Die radikaloperierten und mit Röntgen behandelten Patientinnen, die ohne klinisch feststellbare Metastasen in Behandlung genommen und bis zu ihrem Tode genau beobachtet worden sind und deren unmittelbare Todesursache bekannt ist.

Patientin	Alter	In Behandlung genommen	Lebensdauer	Die zuerst erkannte Metastasestelle	Unmittelbare Todesursache
A. A.	64	14. 8. 36	3 J.	Mediastinum	Lungenmetastase
L. H.	52	15. 2. 37	<1 J.	Rückgrat	Rückgratmetastasen
M. J.	38	5. 3. 37	1 J.	Peritoneum	Allgemeine Karzinose
H. V.	35	28. 1. 39	2½ J.	Lungen	Lungenmetastasen
J. I.	55	23. 2. 39	3 J.	Os occipitale	Gehirnmetastase
H. H.	51	28. 7. 39	<1 J.	Rückgrat und Lungen, gleichzeitig eine kleine Metastase in der Haut und in der Achselhöhle	Lungenmetastasen
S. E.	46	22. 4. 40	2 J.	Lungen	Lungenmetastasen
V. A.	44	22. 4. 40	2 J.	Gehirn	Gehirnmetastasen
N. T.	46	11. 6. 40	1 J.	Leber	Lebermetastasen
K. M.	49	9. 8. 40	1 J.	Lungen	Lungenmetastasen
K. E.	68	7. 10. 41	2 J.	Lungen	Allgemeine Karzinose
K. A.	33	14. 2. 41	1 J.	Knochensystem	Lungenmetastasen
H. H.	44	18. 3. 41	<1 J.	Lungen	Lungenmetastasen
L. E.	53	7. 4. 41	1 J.	In der Haut eine ganz kleine, vereinzelte Metastase, daran nach 3 Mon. Symptome allgemeiner Karzinose	Allgemeine Karzinose
A. S.	31	12. 5. 41	2 J.	Rückgrat und Schlüsselbeingrube gleichzeitig	Lungenmetastasen
T. F.	55	13. 8. 41	<1 J.	Lungen	Lungenmetastasen
S. T.	46	11. 9. 41	1 J.	Lungen	Lungenmetastasen
S. J.	31	23. 9. 41	<1 J.	Rückgrat	Rückgratmetastasen
K. A.	55	15. 12. 41	<1 J.	Lungen	Lungenmetastasen
R. A.	43	16. 12. 41	1 J.	Rückgrat	Rückgratmetastasen
T. M.	34	9. 2. 42	1 J.	Pelvis	Lungen- und Pelvismetastasen
M. A.	56	17. 3. 42	1 J.	Achselhöhle und gleichzeitig Symptome allgemeiner Karzinose, nach einem Monat wurden Lungenmetastasen festgestellt	Allgemeine Karzinose
L. J.	44	16. 6. 42	<1 J.	Lungen und zugleich in der Haut eine kleine Metastase	Lungenmetastasen
S. V.	33	20. 11. 42	<1 J.	Pelvis	Rückgrat- und Pelvismetastasen

Fernmetastasen niedergelassen haben. Doch gibt es auch zahlreiche Fälle, in denen örtliche Metastasen Fernmetastasen verursacht haben können.

Dass man mittels der Strahlentherapie bei der Behandlung von Brustkrebs keine deutlicher hervorstehenden Ergebnisse erzielt hat, beruht, wie auch aus dem von mir vorgeführten Material hervorgeht, darauf dass die zu behandelnde Patientin schon vor Beginn der Strahlentherapie Fernmetastasen gehabt hat, und nicht etwa darauf, dass man durch Strahlentherapie örtliche Metastasen und ihre Entstehung nicht bekämpfen könnte.

De Gaetani und Blothner sowie einige andere Forscher haben

durch Tierversuche nachgewiesen, dass bei der Transplantation von Krebs von einem Tier auf das andere ein Stück von 12,500—5,000,000 Zellen erforderlich ist, damit es in seinem neuen Wirt zu wachsen beginne. Die Widerstandskräfte des Körpers sind so bedeutend, dass sie imstande sind, geringere Krebszellenmengen zu vernichten. Zu einem ähnlichen Ergebnis ist man gekommen, wenn man in Salzlösung suspendierte Zellen von Ehrlichschem Mäusserkrebs parenteral eingespritzt hat. Benutzt man Zentrifugat von Suspension, so braucht man ca. 100,000 Zellen, um bei einem Versuchstier einen Tumor hervorzurufen; bedient man sich aber einer Suspension als solcher, so sind 430,000 Zellen notwendig, damit im neuen Wirt eine Geschwulst wachsen könne.

Das sind zwar Tierversuche, aber manche klinische Erscheinungen weisen darauf hin, dass dasselbe wohl im grossen und ganzen für den Menschen zutrifft. Sonst liesse sich ja nicht erklären, dass Metastasen von Brustkrebs verhältnismässig oft jahre-, ja jahrzehntelang latent bleiben, ehe sie zu wachsen beginnen. Auch das Material des Verfassers umfasst mehrere derartige Fälle. Die eigenen, dem Krebswachstum entgegenwirkenden Kräfte haben diese Metastasen lange Zeit im Zaume gehalten. Wenn aber die Widerstandsfähigkeit des Körpers gegenüber dem Krebs aus irgendeinem Grunde nachgelassen hat, beginnen die versteckten Metastasen plötzlich zu wachsen. Es ist möglich, ja sogar wahrscheinlich, dass die Widerstandsfähigkeit im Organismus Krebskranker herabgesetzt, aber niemals völlig geschwunden ist, wie unter anderem die eben von mir angeführten Tatsachen zeigen. Bei der täglichen klinischen Krebsbehandlung sieht es ausserdem oft so aus, als ob sich bei den Patientinnen nach verhältnismässig langer Latenzzeit ohne unmittelbar vorausgehende allgemeine Aussaat von Krebszellen plötzlich eine allgemeine Karzinose entwickelten könnte. Darauf weist unter anderem der Umstand hin, dass als ein Symptom der allgemeinen Karzinose im Operationsgebiet und in seiner unmittelbaren Nähe oft zahlreiche Hautmetastasen auftreten. Diese Metastasen scheinen lange Zeit latent geblieben zu sein, aber die im Zusammenhang mit der allgemeinen Karzinose auftretende Herabsetzung der Widerstandsfähigkeit des Körpers lässt auch die Entwicklung derartiger örtlicher Metastasen zu.

Es ist wohl möglich, dass im Blut Brustkrebskranker wenigstens zeitweise Tausende von Krebszellen kreisen, aber nach ihrer Festsetzung in irgendeinem Körperteil die Widerstandsfähigkeit des Organismus ihr Wachstum hindert und sie vernichtet. Nur wenn sich an einer Stelle so viel Krebszellen niederlassen, dass die Resistenz des Körpers sie nicht mehr zu vernichten vermag, entsteht eine Metastase oder die latente Anlage zu einer solchen. Ist die Widerstandsfähigkeit des Körpers aus irgendeinem Grunde geschwächt, so können auch geringere Mengen von Krebszellen die Entstehung einer Metastase auslösen.

Verhält es sich auf die oben beschriebene Weise, so muss man in der Brustkrebstherapie danach streben, sich in grösserem Masse als bisher auf die eigenen antikanzerösen Kräfte des Organismus zu stützen und alles zu vermeiden, was diese Kräfte schwächt. Als einen derartigen schwächenden Faktor möchte ich die Radikaloperation nebst allen ihren Folgeerscheinungen ansehen. Betrachten wir die Radikaloperation von diesem Standpunkt aus, so stellen wir erstens fest, wie die Operation selbst schon ein so grosser Eingriff ist, dass sie die Widerstandsfähigkeit des Körpers vorübergehend erheblich schwächen kann, wodurch sich die im Organismus vorhandenen Krebszellen so stark vermehren können, dass er sie nicht mehr zu überwinden vermag. Zweitens stört die Radikaloperation in hohem Masse die Strömung des Lymphplasmas im Operationsgebiet und dessen nächster Umgebung, den Blutkreislauf und die Tätigkeit des Nervensystems. Die in diesem Gebiet gelegenen Metastasen können sich dann besser entwickeln und die Resistenz des Körpers weiter vermindern. Ganz anders verhält es sich, wenn wir uns damit begnügen, eine örtliche Krebsgeschwulst vorsichtig zu entfernen und die lokalen Krebsmetastasen durch starke Röntgentherapie zu vernichten. Dabei bleibt die Widerstandsfähigkeit des Körpers ziemlich unangetastet und kann vielleicht die Entstehung von Fernmetastasen verhindern. Eine solche Therapie kann natürlich nur in den Fällen von Erfolg sein, in denen etwaige Fernmetastasen sich derart im Anfangsstadium befinden, dass die eigenen Kräfte des Körpers ihr Wachstum zu verhindern vermögen, wenn seine Widerstandskraft in keiner Weise geschwächt, sondern durch einfache Exstirpation des Primärtumors und durch Vernichtung örtlicher Metastasen mittels Röntgentherapie eher verbessert wird.

Mit der auf einfache Tumorexstirpation gegründeten Behandlungsmethode sind bisher nur schlechte Ergebnisse erzielt worden. So erwähnt z. B. Gylstorff-Petersen (1944), dass von 16 so Behandelten nach fünf Jahren nur 6 am Leben waren. Von Nohrmans (1943) 8 Fällen waren es nach fünf Jahren 5. Diese schlechten Ergebnisse können darauf beruhen, dass die betreffenden Patientinnen nicht genügend effektive Röntgenbestrahlung erhalten haben.

Diese gegenüber der Radikaloperation viel schonendere Therapie ist keine blosse Theorie mehr, vielmehr ist sie schon von guten Erfolgen begleitet gewesen. Doch ist mein Material noch so klein, dass sich daraus keine sicheren Schlüsse ziehen lassen. Aber die Tatsache, dass von 23 Patientinnen, die mit Tumorexstirpation und Röntgentherapie behandelt worden sind, noch keine einzige an einem Karzinomrezidiv erkrankt ist, berechtigt dazu, diese Therapie schon etwas mutiger, wenn auch vorsichtig und tastend anszuprobieren. Es ist gewiss klar, dass auch diese Methode Enttäuschungen mit sich bringen wird, aber wenn man auf diese Weise doch zu besseren Ergebnissen gelangt, wird damit schon

viel gewonnen sein. Auch wenn die Ergebnisse sich auf demselben Niveau hielten, das man beim Krebs im ersten Stadium durch Radikaloperation erreicht, ist die konservative Therapie dennoch besser, denn sie bewahrt den Kranken vor den durch die Radikaloperation verursachten Nachteilen, die nicht ganz gering sind. Die jetzt in Frage stehende Therapie ist natürlich zunächst auf Karzinome im ersten Stadium zu beschränken, also auf Fälle, in denen keine Axiallardrüsen zu palpieren sind. Auch von diesen Fällen gehören allerdings ca. 29 % in Wirklichkeit dem zweiten Stadium an, denn HARRINGTON hat gezeigt, dass auch in den Fällen, in denen in der Achselhöhle keine tastbaren Drüsen auftreten, die histologische Untersuchung zu 29 % Metastasen in den Axillardrüsen nachweist.

Möglicherweise wird die künftige Forschung zeigen, dass es selbst beim Vorhandensein palpabler Drüsenmetastasen in der Axille angebracht wäre, statt der Radikaloperation nur eine chirurgische Ausräumung der tastbaren Metastasen und vorher und bei Bedarf auch danach eine intensive Röntgenbestrahlung vorzunehmen. Über diese Therapie besitzen wir jedoch noch keine hinreichende Erfahrung, so dass es vorläufig noch nicht geeignet erscheint, sie anzuwenden, vielmehr ist in diesen Fällen eine Radikaloperation am Platze.

Schlussfolgerungen

In den radikaloperierten Brustkrebsfällen, die ohne klinisch feststellbare Metastasen zur postoperativen Röntgenbehandlung gekommen sind, sind die Ergebnisse der Therapie ausserordentlich gut gewesen.

In den radikaloperierten Brustkrebsfällen mit tödlichem Ausgang, die ohne klinisch feststellbare Metastasen Röntgenbehandlung erhalten haben, sind zuerst Fernmetastasen entstanden. Das zeigt, dass der Krebs sich vor der Operation nach den Fernmetastasenstellen ausgebreitet und infolgedessen die Röntgenbehandlung in diesen Fällen keine Möglichkeit gehabt hat, das Behandlungsergebnis zu verbessern. In den wegen Fernmetastasen zur Behandlung gelangten Fällen scheint die Sachlage oft dieselbe zu sein, obgleich da oft örtliche Rezidive auftreten.

In oberflächlichen Metastasefällen ist festgestellt worden, dass sich durch Röntgenbestrahlung eine Dauerheilung erreichen lässt, falls die Kranke keine tiefliegenden Fernmetastasen hat.

Die Behandlung der Karzinommetastasen hat zu ganz schlechten Ergebnissen geführt, denn die Patientinnen sterben an den schon vor der Operation oder im Zusammenhang mit ihr entstandenen Fernmetastasen oder an allgemeiner Karzinose, die nicht durch Röntgenbestrahlung geheilt werden können.

In den mit örtlicher Brustkrebsexstirpation und Röntgen behandelten 23 Fällen sind die Ergebnisse besonders gut gewesen.

Da in beginnenden Brustkrebsfällen mit kombinierter Tumorexstirpation und Röntgenbestrahlung gute Ergebnisse erzielt werden und auf der anderen Seite eine Radikaloperation die Entwicklung von Fernmetastasen nicht verhindern kann, sollte man vorsichtig von konservativerer Therapie zu Tumorexstirpation und starker Röntgenbestrahlung übergehen. Am besten wäre zuerst präoperative Röntgenbestrahlung auf die Brust, dann Tumorexstirpation und schliesslich Röntgenbehandlung der Achselhöhlen- und Schlüsselgrubendrüsen anzuwenden. Die theoretische Grundlage dieser Methode besteht in dem Gedanken, dass dadurch die örtlichen Krebsmetastasen vernichtet werden, ohne die eigene Krebsresistenz des Organismus herabzusetzen. Der Körper vermag dann der von anderswoher in den Organismus verschleppten einzelnen Krebszellen oder -zellgruppen, die sonst den Anfang von Fernmetastasen bilden würden, besser Herr zu werden.

ZUSAMMENFASSUNG

Die Ergebnisse von 384 im Zentralinstitut für Strahlentherapie in Finnland hauptsächlich postoperativ behandelten Fällen von Carcinoma mammae werden vorgelegt. Von 31 Fällen ohne feststellbare Metastasen bei Beginn der Röntgenbehandlung sind 25 (80 %) 5 Jahre symptomfrei geblieben. Von 48 Fällen mit Metastasen sind 5 (10 %) und von 25 inoperablen Fällen nur 2 (8 %) nach 5 Jahren symptomfrei. Unter 23 Früh-Fällen, in denen nur einfache Tumorexstirpation in Kombination mit starker Röntgenbehandlung vorgenommen wurde, ist 1—5 Jahre nach Beginn der Behandlung nur ein Rezidiv beobachtet worden, das jedoch mit der Röntgenbehandlung geheilt worden ist.

Eine Untersuchung über die Todesursache der 194 gestorbenen Patientinnen hat gezeigt, dass in fast allen Fällen der Tod durch Fernmetastasen verursacht wurde, die schon vor oder während der Radikaloperation verschleppt sein dürften und deshalb nicht durch die lokale Röntgenbehandlung erreicht werden konnten.

Angesichts der guten Ergebnisse der konservativen röntgen-chirurgischen Behandlung seiner 23 Früh-Fälle will der Verf. den Vorschlag zur Diskussion stellen, vorsichtig eine mehr konservative Behandlung der Ca mammae in frühen Fällen zu versuchen, anstatt der Radikaloperation, die die allgemeine Krebsresistenz schwächen dürfte. Der Verf. empfiehlt in den Frühfällen von Brustkrebs präoperative Röntgentherapie, einfache Exstirpation des Tumors und danach intensive Röntgenbestrahlung der Achselhöhle und der Klavikulargruben.

SUMMARY

The results of 384 cases of carcinoma mammae which, for the most part, were treated postoperatively at the Central Institute for Radiotherapy in Finland are described. Of 31 cases where metastases could not be demonstrated at the beginning of the roentgen treatment, 25 (80 %) have been free from symptoms for five years. Of 48 cases with metastases, 5 (10 %) and of 25 inoperable cases only 2 (8 %) have been free from symptoms for five years. Of 23 cases in an early stage, in which only a simple extirpation of the tumor, combined with roentgen treatment, has been carried out, only one case of recurrence has been observed 1—5 years after the beginning of the treatment which, nevertheless, has been cured by roentgen treatment.

An investigation as to the cause of death of the 194 patients who have died, has

shown that, in almost every case, death has been caused by distant metastases which must have developed before or during the radical operation and therefore could not have been reached by the local roentgen treatment.

With regard to the good results which have been achieved by the conservative roentgen-surgical treatment in his 23 cases in an early stage, the author would expound the following suggestion for discussion: to try cautiously a more conservative treatment of carcinoma mammae in its early stages instead of a radical operation which tends to weaken the general resistance to cancer. The author recommends in early stages preoperative roentgentherapy, simple extirpation of the tumor and subsequent intensive roentgen treatment of the axilla and clavicular fossa.

RÉSUMÉ

L'auteur présente une étude concernant 384 cas de cancer du sein ayant dans leur majorité subi un traitement post-opératoire à l'Institut Central de Radiothérapie en Finlande. De 31 cas sans métastases constatables au début du traitement roentgenologique, 25 (80 %) sont demeurés sans symptômes 5 ans durant. 5 cas (10 %) sur 48 cas avec métastases et 2 seulement (8 %) sur 25 cas inopérables sont exempts de symptômes au bout de 5 ans. Sur 23 cas, dans lesquels on a pratiqué l'extirpation simple combinée à un traitement intense de roentgen, on a observé une seule récidive de 1 à 5 ans après le traitement, laquelle fut d'ailleurs guérie par les rayons.

Des recherches entreprises pour déterminer la cause de la mort des 194 malades décédées ont démontré que, dans presque tous les cas, la mort a été causée par des métastases lointaines, qui se sont développées avant ou pendant l'opération et n'avaient pu être atteintes par le traitement radiologique local.

Se basant sur les bons résultats du traitement conservateur chirurgical-radiologique combiné de ses 23 cas de cancer récent, l'auteur désire voir discuter la mise à l'essai prudente d'un traitement plus conservateur des cas de cancer récent du sein, au lieu de l'opération radicale qui diminue probablement la résistance de l'organisme au cancer. Dans les cas de cancer mammaire récent, l'auteur recommande la radiothérapie préopératoire et l'extirpation simple de la tumeur suivie d'une intense irradiation de la fosse axillaire et des fosses claviculaires.

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FROM RADIUMHEMMET (CHIEF: PROF. E. BERVEN) AND THE RADIOPHYSICAL INSTITUTE (CHIEF: PROF. R. M. SIEVERT)

STUDIES ON THE BROWN-PEARCE RABBIT-CARCINOMA WITH THE AID OF RADIOACTIVE ISOTOPES[1]

by

A. Forssberg and *F. Jacobsson*

In recent years there have been published a great many investigations of problems relating to malignant tumours, carried out with the aid of artificial radioactive isotopes. These investigations may be said to follow two different lines. On the one hand, radioactive isotopes have been applied in studies of metabolic processes. Very small quantities of a radioactive isotope have then been given together with larger amounts of the same inactive element, their distribution to the organs at different times can then be measured by physical methods. Studies of this kind have been surveyed by HEVESY (1), HAMILTON (2) and others. On the other hand, attempts have been made to use artificial radioactive isotopes in tumour therapy. Some degree of success seems so far to have been attained only in the treatment of forms of leukemia, polycythemia and lymphosarcoma (3).

The present paper deals with a study of the Brown-Pearce rabbit carcinoma. Of the animal tumours generally used in cancer research, this one possesses a rather outstanding capacity for forming metastases in almost any part of the body, and thus affords good opportunities of studying the distribution of injected isotopes to metastatic and normal tissues. On the other hand the real nature of the Brown-Pearce rabbit carcinoma seems to be a matter of dispute. The metastases form rapidly growing masses, the living cells of which are mostly situated peripherally, or around the blood vessels. The rest of the tumour often consists of a necrotic mass, infiltrated by lymphocytes and plasma cells. For histological details the reader is referred to BROWN and PEARCE (4) and CASEY (5). According to CASPERSSON and SANTESSON (6) there are also

[1] Submitted for publication, March 1, 1945.

marked differences between the peripheral, living zone and the necrosis in protein metabolism.

KALLÓS (7) and CASEY (5) have published careful investigations of the distribution of metastases in different organs. In Kallós' material the carcinoma obviously took in about 80 % after intratesticular grafting on grayish or brown rabbits. Later on metastases could be demonstrated in all the diseased animals, in some organs almost without exception, and in most of the others in more than 50 %. The spleen and the bones seem however seldom affected.

The development of the primary tumour and the distribution of the metastases was completed rather quickly. As a rule the primary tumour could be felt some 10—14 days after the grafting. The metastases developed within the next one or two weeks and the animals then soon died. Some of our material deviated from this time schedule, the whole process being more protracted. Nevertheless the critical time, i. e. the time it takes metastases to spread and develop may be said to be very short — a few weeks. In practice it would consequently be possible to maintain a rather high radioactive regime in the organism during that critical time without consuming too large quantities of radioactivity. It should thus also be possible to ascertain whether the radiation has any prophylactic effects or not.

Before any possible therapeutic use of artificial radioactivity can be investigated, it will be necessary to ascertain the relative distribution of the radioactive isotope to different organs, normal and neoplastic. We have used radioactive phosphorus (^{32}P) in our investigations. Rather small quantities were injected and analyses made at different intervals after the injection in the following way:

Methods: A pressed mash of growing tumour was grafted on the testes of 6—8 months old, greyish or black male rabbits. Albino rabbits should be avoided (see BROWN-PEARCE and KALLÓS), as a considerably lower percentage of them »take» the tumour (only 37 % positive according to KALLÓS).

The radioactive phosphorus,[1] in the form of a solution in water of Na_2HPO_4 which had been made isotonic and at pH = 7.2 was injected in the auricular vein. We gave a single dose of 0.1 mC to each rabbit at slightly varying times after the inoculation (Table 1, Column 2). The animals were killed and analysed at the times said in Column 3.

Weight samples of the tumours and of the normal organs were then completely dissolved to a clear, yellow liquid in conc. H_2SO_4 and a few

[1] We are much indebted to the Institute for physics, Royal Academy of Science, Stockholm, for kindly supplying the ^{32}P.

Table 1.

Radioactivity: Fraction of injected quantity (0.1 mC) × 10−4 in one gram wet weight

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1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rabbit No.	Time in days between:		Metastases[1]	Normal samples of:											Samples of some other organs[3]		Ratio:	
	Grafting and injection	Injection and death		Liver[2]	Kidney[2]	Spleen	Suprarenal gland[2]	Mean of column 5—8	Whole blood	Bone-marrow	Lungs	Muscle	Ribs	Femur	Metastases	Normal parts	Column 16 / Column 9	Column 16 / Column 17
1	39	6	+++	[4]1.09	[4]1.12	—	—	—	0.49	0.46	0.79	0.28	2.76	0.32	1.72	1.09	—	1.58
2	29	11	+++	1.40	1.22	1.12	1.44	1.30	0.42	0.91	0.98	0.53	13.6	4.03	0.98	0.46	1.33	2.13
3	29	17	+++	1.05	0.98	0.88	0.98	0.98	0.32	0.88	0.59	0.81	11.4	4.30	1.05	0.49	0.93	2.14
4	29	24	++	0.95	0.95	0.84	1.09	0.95	0.07	0.60	0.80	0.74	11.3	2.98	0.74	0.49	1.28	1.51
5	—	10	not grafted	2.31	2.06	2.06	2.66	2.28	0.21	0.74	1.43	1.05	4.24	1.43	—	0.39	—	—
6	—	24	not grafted	0.91	0.84	0.88	1.19	0.95	0.13	0.28	0.75	0.70	27.0	8.03	—	0.42	—	—
7	20	4	++	5.81	4.76	5.95	5.68	5.54	0.35	1.58	4.06	0.67	5.11	3.15	5.40	1.05	1.03	5.14
8	20	6	+++	3.60	3.18	4.14	4.45	3.85	0.53	1.64	2.80	1.33	14.0	3.78	4.13	1.54	0.93	2.68
9	24	2	++	8.55	6.10	9.11	6.51	7.56	0.88	5.89	3.88	0.98	34.5	6.45	5.95	1.12	1.27	5.31
10	—	3	not grafted	7.54	6.59	9.05	4.94	7.00	1.26	6.55	4.96	0.88	20.7	16.3	—	2.10	—	—
11	22	3	+++	6.45	5.57	7.50	6.59	6.51	0.95	3.74	4.24	0.91	16.7	6.16	6.86	2.66	0.95	2.58
12	—	4	not grafted	6.34	5.81	5.67	6.45	6.06	0.95	2.20	3.18	0.88	16.2	6.69	—	1.79	—	—
13	39	1	0	8.12	7.85	5.70	5.08	6.70	1.72	3.96	4.51	1.02	16.7	17.3	—	1.43	—	—
14	34	1	+	7.99	9.60	9.11	9.40	9.04	2.17	2.56	6.36	1.82	15.1	2.80	9.11	1.68	0.99	5.42
15	34	1	0	11.1	12.5	9.15	6.20	9.75	2.48	—	5.99	1.61	12.7	3.22	—	—	—	—
16	34	3	0	6.45	6.37	8.70	5.50	6.72	1.09	—	5.19	1.78	26.6	9.05	—	—	—	—
17	34	3	+	7.78	9.15	10.7	11.6	9.80	1.54	6.24	6.75	2.03	29.9	11.9	8.90	1.82	1.10	4.97
18	42	1	0	8.20	8.48	8.62	6.72	7.99	1.54	—	3.43	0.91	15.5	6.69	—	—	—	—
19	42	1	+	6.76	14.6	7.07	5.25	8.40	1.36	—	3.54	1.05	10.8	8.55	5.95	1.22	1.41	4.97
20	10	9	+	4.03	4.13	4.16	5.29	4.41	—	2.38	3.29	3.29	15.2	5.25	3.07	1.19	1.44	2.60
21	13	39	0	0.88	0.81	1.16	1.16	0.98	0.13	—	0.93	0.98	11.3	19.1	—	—	—	—
22	—	7	not grafted	3.22	3.12	4.06	3.78	3.55	0.41	1.50	2.70	1.29	29.6	12.9	—	—	—	—
23	22	30	+	0.90	0.65	0.97	1.83	1.09	0.12	0.31	0.70	0.74	7.6	2.78	1.39	0.36	0.78	3.90
24	—	38	0	0.47	0.59	0.75	0.97	0.70	0.13	—	0.44	0.59	12.5	8.30	—	—	—	—
			Mean	4.83	5.03	5.11	4.55	4.87		[5]2.26					4.73		1.12	

[1] +++ = very abundant. ++ = abundant. + = scanty. 0 = no metastases, or too scanty for analyses.
[2] For activity in metastases see Fig. 1.
[3] Viz: Diaphragm, pleura, peritoneum, omentum, mesentery, intestines, testis and lymph nodes.
[4] These values are not included in the means, as analyses for spleen and suprarenal gland are missing.
[5] From rabbits with metastases.

drops of H_2O_2. The radioactivity was measured with a Geiger-Müller counter and an automatic counting device. The impulses were registered as follows: The G-M-counter was dipped into the liquid in a special glass to a fixed mark, and the number of impulses, corrected for leakage, computed. The weights of the analysed samples were adjusted so as to obtain statistically reliable results. The activity of the unknown samples was correlated with a concentrated sulphuric acid ^{32}P-standard from the solution used for the injection. The results could thus be expressed as fractions of retained radiophosphorus per gram of wet weight at the time of death. The method was first tested and its reliability confirmed with known ^{32}P-solutions of different strengths.

Samples of metastases from all affected organs of the animals and from »normal», i. e. unaffected, parts of the same organs were taken. Besides, analyses were made of the radioactivity of whole blood, lungs, ribs, femur, bone marrow and muscle, the values obtained being stated here without further discussion. On a few occasions we also analysed some other organs, viz. intestines, pancreas, thyroidea, salivary glands and cartilage. As the space is limited they have not been tabulated here, however, particularly as they are of minor interest in this connection. In order to ascertain the difference in the assimilation of phosphorus in »normal» parts of organs partly infiltrated with metastases, and in the same organs from healthy animals, some rabbits that had not been grafted were also analysed. The phosphorus metabolism of grafted animals, especially when severely affected, might conceivably show abnormal features. This seems so far not to have been the case, as the corresponding values did not differe significatively. In Fig. 1 it will be seen that the values for the liver, kidney, spleen, and suprarenal gland decline at the same rate with the time, independent of their origin in the above-mentioned respects.

The radioactivity in the not affected parts of the said organs show great resemblance to one another (Table 1, Columns 5—8). If we take the mean of all the analyses of each organ, we get the values 4.83, 5.03, 5.11 and 4.55; the differences are insignificant. Column 9 gives the means of the liver, kidney, spleen, and suprarenal gland analyses for each rabbit and in Fig. 1 these means are plotted against the time between the injection and the death. The slope of the curve indicates a rather rapid excretion of the absorbed phosphorus during the first days after an injection. Later on the rate of excretion diminishes considerably. From approximately the tenth day there seems to be a loss of activity owing to removal of only a few per cents a day of radioactive phosphorus from these organs.

Metastases frequently appeared in these organs, except in the spleen, in our material. The radiophosphorus values of every single analysis of

these metastases are also plotted in Fig. 1. Obviously they do not differ appreciably from the general slope of the curve. We may thus say that the phosphorus metabolism of the organs under discussion and the metastases in the same organs are on the whole of the same order of magnitude.

The Brown-Pearce carcinomas produce, as pointed out above, metastases in a great many other organs. They were rather frequently

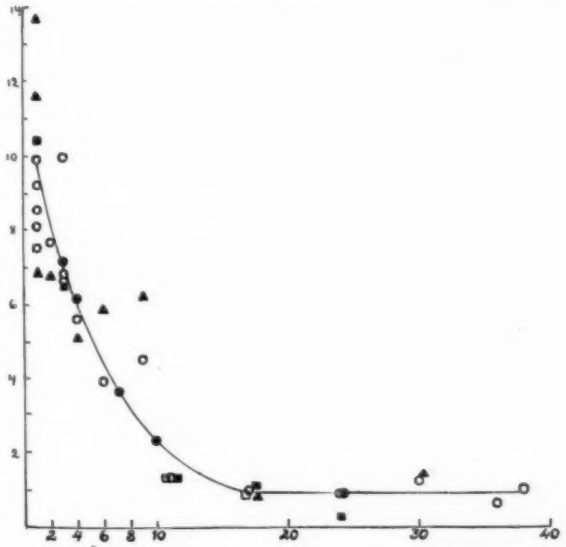

Fig. 1. Radioactivity in normal tissues and metastases from liver, kidney, spleen and suprarenal gland. Normal samples from grafted (○) and not grafted (●) animals. Metastases from liver (□), kidney (■) and suprarenal gland (▲). Abscissa: Time in days between injection and death. Ordinate: Radioactivity as fraction of injected quantity (0.1 mC) per gram wet weight.

found in the following tissues: pleura, pericardium, diaphragm, peritoneum, omentum, mesentery, lymphatic organs, testis (the ungrafted side). In all, we made some 200 analyses of metastases and normal parts from these organs. An inspection of the results led to the conclusion that they may be discussed here as one group, as the separate analyses indicated that the distribution to the said organs did not differ greatly. We may accordingly drop the space-demanding tabulation of the whole experimental material, and give in Columns 16 and 17 the mean of the metastase and normal values for every rabbit. For every analysis on a metastasis, a sample from the corresponding »normal» tissue was also

taken. The absolute radioactivity values may of course vary with the time. The ratio

$$\frac{^{32}P \text{ concentration in the metastases}}{^{32}P \text{ concentration in the corresponding »normal» tissues}} \quad \text{(Column 19)}$$

deviates however, significatively from unit, which indicates the presence of considerably more ^{32}P in the metastases.

In Fig. 2 this ratio is plotted against the time between injection and death. During the first days after a single dose, an average of 5

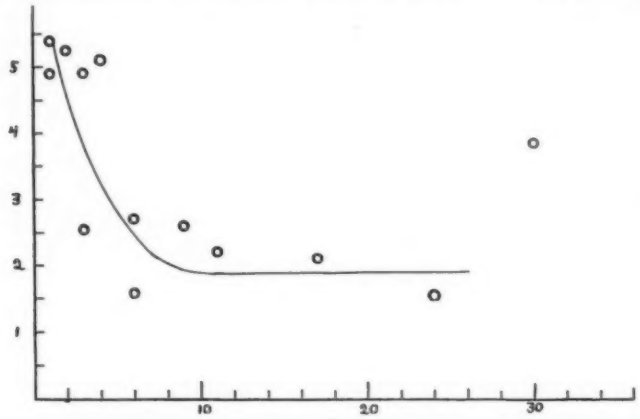

Fig. 2. The ratio: $\frac{^{32}P \text{ concentration in metastases}}{^{32}P \text{ concentration in the corresponding normal tissues}}$ in the organs enumerated in Table 1, Column 16 and 17. Abscissa as in Fig. 1.

times as much radioactive phosphorus will be found in the tumour samples as in the »normal» organs. Between the 4:th and the 6:th day the loss of activity in the metastases is apparently faster. From the 10:th day the curve runs approximately parallel with the X-axis, indicating equilibrium in the phosphorus excretion. From that time the metastases appear to hold about 1.5 to twice as much ^{32}P for at least some weeks onwards. An apparent exception from this offers the analyses on rabbit 24, which are plotted in the curve at 30 days. The ratio is here about 3. The progress of the disease was in this case unusually protracted, however, and the dissection about 7 weeks after the grafting showed that the metastases were very small. This is a stage which in the rest of the material was reached very soon after the injection of ^{32}P.

It is also interesting to compare the phosphorus metabolism in the metastases with that in the four normal organs mentioned above.

(Table 1, Columns 5—8.) From column 18 this ratio will be found not to deviate much from unit-value, the mean of all the values being 1.12. Metastases may then, irrespective of their site, be said to store about the same amount of radioactive phosphorus, and as much as organs where the metabolic rate is high, viz. kidney, liver, spleen and suprarenal gland. The rates of excretion in both instances are also approximately the same. The results agree with those of JONES, CHAIKOFF and LAWRENCE (8), who found that lymphoma, lymphosarcoma and mammary carcinoma in mice had a phosphorus metabolism reminiscent of that of the normal liver and kidney. From a practical point of view the results may be said to suggest, that it would probably be difficult to »charge» the metastases with a therapeutically sufficient degree of radioactivity by successive injections of ^{32}P without great risk of damaging these organs. Further, a comparison of Columns 11 and 16 in Table 1 likewise shows that the ratio of ^{32}P-concentration in the metastases to that in the bonemarrow with its radiosensitive, blood-forming elements averages only about 2, a rather insignificant difference. The conclusions in an investigation of the distribution of radiophosphorus made at Radiumhemmet point the same way in some cases of cancer in man.

Certain evidence of the distribution of radiophosphorus can also be obtained by phothographic means: Parts of tumours were fixed and cut in 10 μ thick sections. Of two subsequent sections one was stained, and from the other autoradiograms were taken in the following way: The sections were pressed tightly on photographic plates (Agfa Autolithe or K-plates) covered with a very thin cellophan layer. 2—3 days exposure generally proved sufficient. Fig. 3 illustrates some of the results. From the figure (A and B) may be seen that the unequal distribution of radioactivity to neoplastic and the surrounding normal tissue can be visualized. The accumulation of radiophosphorus in growing metastases of the peritoneum and the lymph nodes is evident. Fig. C gives a large tumour from the omentum. The parts in the autoradiogram marked by a line, proved on the stained section to be completely necrotic, and apparently the radioactivity is also lower there than in the growing parts. Probably, however, the inequality of the radiation from necrotic and non-necrotic parts is somewhat exaggerated. As will be shown later, there is a marked difference between necrotic and non-necrotic tumour tissue. In the former the phosphorus is chiefly bound in an acid-soluble form, and very likely parts of it have been washed out during the fixation. Thus the picture probably mainly visualizes the difference in nucleoprotein-phosphorus content.

In order to ascertain if there are any pronounced differences in the phosphorus absorption by growing and necrotic parts of the tumours, we also made some analyses for that purpose.

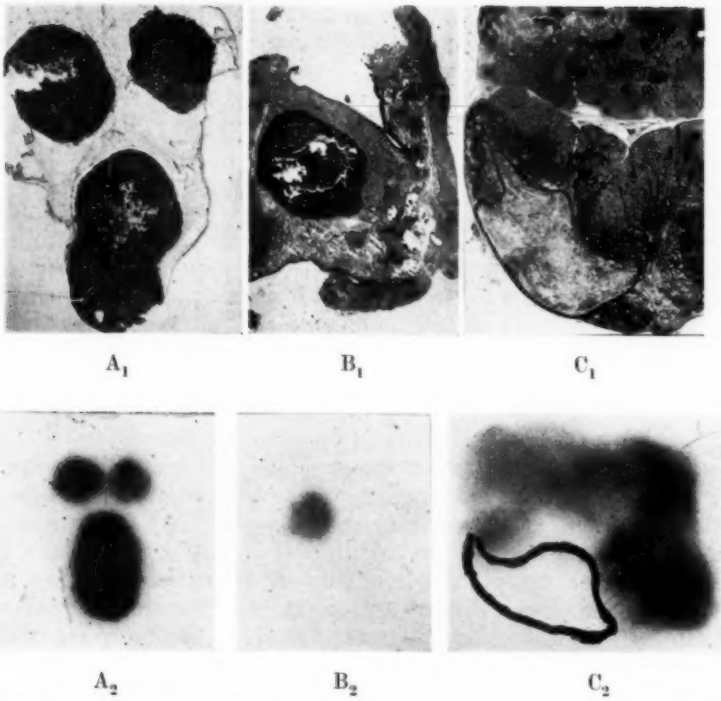

Fig. 3. A_1 Stained sections of three growing metastases from the peritoneum, surrounded by normal tissue. A_2 Autoradiogram from the next section. B_1 Stained section of a metastasis in a lymph node. B_2 Autoradiogram from the next section. C_1 Stained section from a metastasis from the omentum. Large necrotic part ringed in. C_2 Autoradiogram of the next section; necrotic part with less radioactivity.

Table 2.

Days between injection and death.

	4	6	11		17			30
	Testis	Peritoneum	Diaphragm	Peritoneum	Diaphragm	Omentum	Peritoneum	Omentum
Actively growing part....	5.80	3.92	1.04	0.91	1.08	1.15	1.06	0.63
Necrotic part.....	3.12	2.98	0.99	0.55	0.80	0.74	0.88	0.74

Tumour masses from the organs were divided into two parts and analysed. A sharp distinction between growing and necrotic substance is, however, difficult to attain.

With one exception the figures indicate a certain, though not much higher concentration in the growing parts of the tumour. Apparently this holds good irrespective of the site of the metastasis. The ratio $\frac{^{32}P \text{ in growing tumour}}{^{32}P \text{ in necrotic tumour}}$ keeps between 1 and 2, and is possibly a trifle higher shortly after the injection, as would be expected. According to KENNEY (3) more radioactive phosphorus is also found in actively growing areas of osteogenic sarcoma than in regions where the tumour has degenerated.

From the chemical point of view, one may ask in which part of the cell, or in which chemical form, the injected phosphorus is stored. MARSHAK (9) has shown, that the nuclei of malignant cells store more ^{32}P than those of normal cells. Moreover, the ratio $\frac{^{32}P \text{ in nucleus}}{^{32}P \text{ in plasma}}$ was higher in malign than in normal tissue. This seems to be connected with the augmented rate of cell division in the former case.

ERF, TUTTLE and LAWRENCE (10) fractioned ground lymphomas and normal tissue from mice into a »lipoid fraction», an »acid-soluble fraction», and a »nucleo-protein fraction». A comparison between neoplastic and normal tissues showed that the greatest difference was to be found in the nucleo-protein fraction, the neoplastic tissues containing 3—4 times as much phosphorus as normal tissue. A work of ERF and TUTTLE (11) shows, however, that the distribution to the said fractions may vary considerably in different cells or tissues. They found that in red blood cells from patients with leukemia and polycythemia the retention in the nucleoprotein fraction reached a maximum approximately 2 days after injection, and that the values fell after that time. The lipoid phosphorus fraction increased, on the other hand, steadily during the first 4 days. It must also be remembered that the radiation from the injected ^{32}P-source may influence the distribution of phosphorus in the three fractions. Investigations by ABELS, KENNEY and associates (12) seem to show this. An increase of the acid-soluble phosphorus fraction was shown to take place after a roentgen irradiation of about 3 r of the whole body.

Some fractional analyses were made on metastases and normal tissues of our material. Ground samples were extracted 4 times with 50 cc. of a 3 : 1 alcohol-aether solution. The rest was shaken three times with 50 cc. cold 5 % trichloracetic acid, and the residue from this was burned in conc. H_2SO_4 and a few drops of H_2O_2. Thus we had the material

Table 3.

Radioactivity as in Table 1.

Analyse No.	Days between injection and death	Tissue	Lipoid-fraction	Acid-soluble fraction	Nucleoprotein-fraction	Ratio: $\frac{^{32}P \text{ in metastases}}{^{32}P \text{ in normal tissue}}$ for: Lipoid-fraction	Acid-soluble fraction	Nucleoprotein fraction
1	1	Growing parts of metastases in omentum	1.40	3.33	5.04	2.0	4.75	11.1
2		Normal omentum	0.70	0.70	0.46			
3	3	Young metastases in omentum	1.23	1.93	3.48	1.45	2.0	11.1
4		Normal omentum	0.84	0.95	0.31			
5	3	Metastases in the peritoneum	0.42	0.70	3.22	5.5	0.85	13.1
6		Normal peritoneum	0.08	0.81	0.25			
7	1	Primary, not necrotic tumour in right testis	1.23	3.64	3.18	1.6	2.5	23.1
8		Normal, left testis	0.77	1.47	0.14			
9		Necrotic tumour mass from testis	0.52	8.73	1.45	0.67	5.9	10.6
10	30	Necrotic tumour mass from testis	0.32	1.49	1.00	0.66	18.0	1.92
11		Normal testis	0.49	0.08	0.52			
12	30	Necrotic tumour mass in omentum	0.26	0.35	0.82	2.16	> 7	3.90
13		Normal omentum	0.12	<0.05	0.21			

roughly separated in a »lipoid fraction» containing the fats, an »acid-soluble fraction» containing most of the inorganic dissociable phosphorus, and a »nucleoprotein fraction» containing the greater part of the organically fixed phosphorus. All fractions were correlated to known standard solutions in the same liquids. The results are given in Table 3.

A survey from that point of view of the distribution of ^{32}P to neoplastic and corresponding normal tissue shows that the by far greatest part of the increase in radioactivity in the metastases falls on the nucleoprotein fraction. These results agree with those of the above authors and hold good for actively growing tumours, probably rather independently of their sites. (Cf. analyses 1—8.) Old, necrotic tumours seem to alter the picture. In connection with the decomposition of the tissue an equally great or even greater part of the activity is often found in the acid-soluble fraction. (Cf. 9—13.) The ratio:

$$\frac{^{32}P \text{ in nucleoprotein fraction}}{^{32}P \text{ in acid-soluble fraction}}$$

which for growing tumours is ≥ 1, diminishes in some cases of necrotic tumours to $\backsim 0.1$—0.2.

To sum up the experiences of these investigations, it may be said that the possibility of destroying or stopping the development of *already formed* metastases of the Brown-Pearce tumour without damaging vital

parts of the body does not seem great. This is evident from the fact that the ratio of radio-phosphorus absorbed in metastases to that in organs with a high metabolic rate, such as liver, kidney, spleen and suprarenal gland, is about unity. As seen from Table 1 the difference in the absorption in metastases and in bone marrow is in most cases not great either. The chances of a severe damage to the blood-forming elements of the bone marrow would thus be considerable. Matters may perhaps be more favourable if some sort of prophylactic therapy is tried, i. e. if the spreading of the metastases could be prevented. As was pointed out in the introduction, the time taken by the metastases to spread through the blood or lymph organs is generally remarkably short, thus making such an experiment possible in practice. This point will next be investigated.

This investigation was aided through a grant from P. A. Ljungbergs' fund to one of us. (F. J.)

SUMMARY

The distribution of intravenously injected radioactive phosphorus (^{32}P) on rabbits, grafted with the Brown-Pearce carcinoma, has been investigated. The metastases were shown to absorb on an average as much ^{32}P as the liver, kidney, spleen and suprarenal gland, rather independently of their site in the organism. The rate of excretion after a single dose was also the same. Young, still growing metastases generally hold more ^{32}P than when old and necrotic. In the former the greatest part of the radiophosphorus is present in an organic form (nucleo-protein phosphorus); in the latter an equally great or even greater quantity in acid-soluble form.

From the therapeutical point of view the results seem to indicate that it would hardly be possible to attain a concentration of ^{32}P in the metastases, sufficiently high to stop their development, without damaging the said organs or the bone marrow. It might perhaps be possible, however, to prevent the origin and spreading of the metastases by a concentrated therapy during the earliest development of the disease. Experiments to that end will be made.

ZUSAMMENFASSUNG

Es wurde untersucht, wie sich radioaktiver Phosphor (^{32}P) in Kaninchen mit Brown-Pearce Karzinom verteilt. Unabhängig von der Lage der Metastasen im Organismus nahmen diese etwa gleich grosse Mengen ^{32}P wie Leber, Niere, Milz und Nebenniere, auf. Die Geschwindigkeit der Wiederausscheidung war ebefalls die gleiche. Noch zunehmende Metastasen enthalten gewöhnlich mehr ^{32}P als nekrotische. In ersteren ist die grösste Menge des radioaktiven Phosphors organisch gebunden, in letzteren ist oft eine gleich grosse, wenn nicht sogar eine grössere Menge ^{32}P in säurelöslicher Form enthalten.

Die Möglichkeit, in schon entstandenen Metastasen eine genügend grosse Konzentration von ^{32}P zu erhalten, um die Entwicklung der Metastasen zurückzuhalten ohne die genannten Organe oder das Knochenmark zu schädigen, erscheint schwierig. Die Möglichkeit, die Entstehung der Metastasen mittelst Therapie im frühzeitigen Stadium der Krankheit zu verhindern, ist vielleicht vorhanden. Dies wird Gegenstand einer nächsten Untersuchung sein.

RÉSUMÉ

Un examen a été fait sur la répartition du phosphore radio-actif (^{32}P) par injection intra-veineuse, chez des lapins inoculés de carcinome Brown-Pearce. Les métastases ont absorbé les ^{32}P, plus ou moins indépendamment des organes dans lesquels elles se trouvaient, en quantités à peu près égales à celles absorbées par le foie, les reins, la rate et les glandes supra-rénales. La vitesse avec laquelle l'excrétion d'une seule et unique dose a eu lieu, était aussi la même. Les métastases plus jeunes et encore croissantes, prennent un peu plus de ^{32}P que les plus vielles métastases, déjà nécrosiques. Dans les premières, le phosphore se retrouve, pour la plupart, sous une forme organique (phosphore de nucléo-protéine), dans les dernières, il se retrouve souvent, en quantité égale ou supérieure, soluble dans l'acide.

Au point de vue thérapeutique, les résultats semblent indiquer l'invraisemblance de pouvoir atteindre une concentration de phosphore radio-actif suffisante dans les métastases pour arrêter leur développement sans endommager l'organe en question ou la moëlle des os.

Il existe cependant peut-être la possibilité d'empêcher, de façon prophylactique la formation et la propagation des métastases sur un développement de tumeur à l'état primaire, par une thérapeutique concentrée. Ceci sera l'objet d'un examen ultérieur.

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FROM THE ROENTGEN CLINIC OF THE STATE HOSPITAL, COPENHAGEN
(CHIEF: PROF. P. FLEMMING MØLLER, M. D.)

THE ROENTGEN PICTURE OF THE TABETIC ARTHROPATHIES AND AFFECTIONS OF BONES[1]

by

P. Flemming Møller

Twenty-five years ago the diagnosis of the tabetic affections in bones and joints was very frequent in roentgenologic hospital services of any magnitude, but modern syphilis therapy and the greatly diminishing frequency of syphilis in the years before the present war had of late resulted — in Denmark, at least — in these affections being rarely met with. With the greatly increasing number of fresh syphilis cases in the last few years it is to be foreseen, however, that in the time to come they may again become more frequent; and as the younger generation of radiologists, at least, owing to the circumstances has not had occasion to become familiar with the changes in bones and joints that may be caused by tabes dorsalis, and perhaps have never even seen roentgen pictures of such changes, I have thought that it might be well to recall them to memory.

In order to illustrate these changes I have therefore collected the rather considerable material of old films of tabes dorsalis cases which still exist in the archives of the State Hospital. For the roentgenologic picture of the tabetic changes in the bones is as a rule so characteristic that when one has once got to know it the diagnosis is usually easy. And it is all the more important to be familiar with it because the diagnosis of tabes dorsalis is often first established at the roentgen examination.

It is always said that the first description of the clinical picture of the tabetic arthropathies was given, in 1868, by CHARCOT, and in many places the affection is therefore also called »Charcot's joint». The priority rightly belongs, however, to MITTCHELL, who had described it already thirty-seven years before, in 1831; but his paper attracted little attention and was in time forgotten. The clinical picture was thus known long before

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the advent of roentgenology, but here, as in many other fields of pathology, the roentgen examination later became a valuable aid for the early diagnosis and to the understanding of the development of the changes observed.

With regard to the pathogenesis of the roentgenologic changes it was formerly a subject of frequent discussion whether the tabetic changes in the joints were a direct manifestation of the syphilis or a result of the nervous affection due to the latter. The question is all the more difficult to answer because a not particularly pronounced tabetic change, for instance in the knee, may remind somewhat of a true gummous osteitis. That it is absolutely not a question of gumma has, however, been fully proved by the histologic examinations; but this is also about as far as we have come as regards the explanation of the pathologic changes since KREDEL and others in the eighties and nineties of the last century tried to shed some light on the subject.

It is probably agreed by all, however, that trophoneurotic or trophic vasomotoric disorders resulting from the lesion of the spinal marrow play a rôle for the production of the changes, and also that the background for these is the same as for the changes that may be found in bones and joints especially in syringomyelia, and also, though rarely, in other affections of the spinal marrow, such as myelitis, postencephalitis, paraplegia, lesions of the dorsal roots, and on the whole in affections of the central nerve system. There is this difference, however, between syringomyelia and tabes dorsalis, that in tabes, which is an ascending degeneration of the posterior column, specially the joints of the lower extremities become affected — namely in 80 per cent of cases; whereas in syringomyelia, which is mostly localised to the cervical marrow, it is chiefly — also in 80 per cent of cases — the upper extremities. The pathologic changes in the two diseases are morphologically identical and they both give precisely the same roentgenologic picture; there is nothing in this which enables one to distinguish between the two; and in syringomyelia, too, spontaneous fractures may occur, also of the lower extremities.

Histologically, there has not with certainty been demonstrated any osseous alterations that might account for the development of the changes, especially for the fragility of the bones. BLANCHARD and REGNARD have described, though, a dilatation of the Haversian canals which, according to them, may become confluent and form large cavities, and in which they found abundant fat-cells. These changes were particularly pronounced inwards toward the medullary cavity, and when they extended out towards the periphery the bone would there be porous, rather like a sieve. REGNARD also thought that on chemical examination he found a decrease of phosphate content and increase of fat. The two authors believe that this is the cause of the brittleness of the bones. I have not been able to

Fig. 1 a. Fig. 1 b.

find any confirmation of their observations by other investigators. Roentgenologically, nothing abnormal that might confirm them can be demonstrated in the bones, especially no calcareous atrophy or change of the osseous structure. The latter is to all appearances entirely normal. Roentgenologically as clinically, the spontaneous fractures and the affection in the joints are the two principal symptoms, but the question is whether the fragility of the bones is not the primary in all the changes. I shall come back to this in the following.

The frequency of the spontaneous fractures was pointed out among others by KREDEL (1888), who found 73 such fractures in a material of 257 cases of arthropathies. They may occur at any stage of tabes, and often it needs only a very slight trauma to produce them. Even so slight a strain as caused by the pulling on of a boot may cause a fracture in the lower extremity. But it is characteristic of these tabetic fractures that they on account of the anesthesia are painless, or nearly so. The patient therefore gives no heed to the matter and continues to walk on the leg; what, of course, greatly contributes to aggravate the lesion at the point of the fracture. The tabetic fractures of the long tubular bones are therefore as a rule very much splintered, and where a fracture of that character is caused by a comparatively slight trauma the possibility of tabes dorsalis must always be borne in mind. (Fig. 1 a and b.)

Fig. 2.

Fig. 3.

It is well known that the fracture may be the first symptom of the disease. This was the case, for instance, in a patient who was recently admitted to the State Hospital. He had stumbled and fallen in the street, but had been able to get up and walk home; but the next day he was suddenly unable to stand on the leg, and at admission there was found a much splintered fracture, which we at once suggested might be due to tabes. The patient was found to have highly positive Wassermann reaction and, indeed, tabes dorsalis.

The weight on the injured bone moreover often results in extensive lesions of the surrounding soft tissues. These again lead to copious, deep hemorrhages with resulting large soft-tissue tumors, which owing to the bleeding assume a faint bluish color under the tightened skin. This picture sometimes gives rise to confusion with sarcoma, especially because the patient does not always at once realise that there is a fracture, and therefore fails to call the physician until some time has elapsed.

These severe lesions of bones and soft tissues not infrequently result in enormous, strong callus formations and extensive myositis ossificans; for the fractures generally have a tendency to heal well. Sometimes, however, they heal only slowly, or not at all. This is particularly the case with the frequent fractures of the neck of the femur. The appearance of these is, as a rule, very characteristic, the fracture being situated very high up, right below the head (Fig. 2). It looks as if the latter had been chiselled off by striking against the upper rim of the acetabulum, and unless the fracture is associated with tabetic arthropathy there is as a rule — in contrast to what is the case in other tabetic fractures — very

Fig. 4 a.

Fig. 4 b.

little reaction on the part of the surrounding soft tissues. These collum fractures are often not recognised as such, and the patient may go about for a long time with the fractured hip without the condition being correctly diagnosed. This perhaps accounts for the fact that the fracture surfaces in these cases so often present a quite smooth, polished-off appearance.

With these collum fractures there is also a marked tendency to resorption and complete disappearance of the severed caput (Fig. 3), so that it looks as if the end of the joint had been resected. Such a resorption of the end of the joint may also be seen in other articulations, especially in the elbow and the shoulder, but it is most frequent in the hip (Figs. 4 a—4 b). The phenomenon is probably due to the special conditions of circulation and nutrition in the end of the joints, particularly in the hip, and can probably also occur in other diseases than tabes. Thus I have once seen the almost complete resorption of the head of the femur following a simple fracture of the collum with pin-osteosynthesis and secondary aseptic necrosis.

Among the spontaneous fractures must also be reckoned the changes which may occur in the spinal column (Fig. 5. — In this case there were also changes in the hip.) The fractures of the vertebrae often result in very curious deformations and dislocations of the spinal column, like a kind of spondylolisthesis; and enormous formations of new bone occur, with great increases of the volume of the vertebrae, which must be seen

Fig. 5.

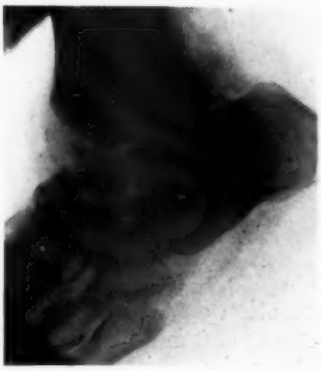

Fig. 6.

on the same background as the large formations of new bone in the other spontaneous fractures (Fig. 6).

Also fractures in the foot are often seen, especially of the talus and the calcaneus. They may occur either isolated or in connexion with other fractures. On the whole, the fractures are not infrequently multiple. Sometimes the lower jaw, too, is involved, and the changes show themselves there also in the form of small fractures with secondary destruction of the alveolar process and athrophy; the teeth fall out, and often sequestra are cast out.

The *tabetic affections in the joints* (Fig. 7 a and b) present a multivarious picture, characterised on the one hand by very considerable destruction of the ends of the joints, on the other hand by enormous, luxuriant new bone formations, which may completely surround the joint like a spongy mass (Fig. 8 a—8 b). Besides, numerous free joint-mice are formed (the well-known »bag of nuts»), and large, peg-shaped bony outgrowths — calcified myositis — so that the joint and its surroundings may assume quite phantastical shapes. These changes may take a short and rapid course or be more chronic, but it is important to know that also

Fig. 7 a.

Fig. 7 b.

Fig. 8 a.

Fig. 8 b.

the affection in the joint may occur at a time when neither the patient nor the physician is aware of the existence of tabes.

Sometimes a swelling and accumulation in the joint is the first objective symptom, in other cases a period of slight »rheumatic» pains may precede the actual onset; sometimes, but not always, there will be some slight preceding trauma, a sprain or the like. But most often the symptoms

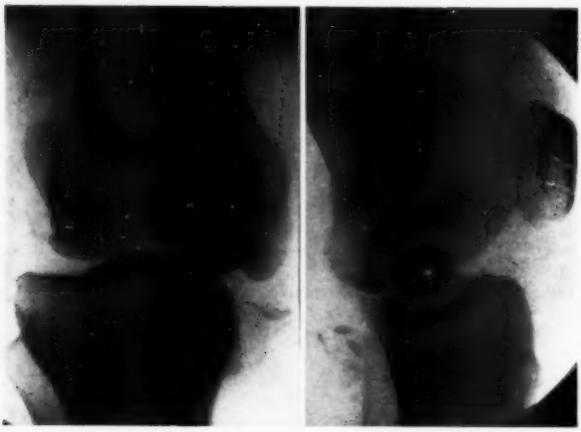

Fig. 9 a. Fig. 9 b.

begin suddenly with a large accumulation in the joint and severe deformation of the latter; and just as in the spontaneous fractures there is marked analgesia and an absence of inflammatory phenomena and fever, so that the patient does not at once think of consulting a physician, but continues to walk on the leg. This, of course, results in the condition getting worse; and then, gradually, the very characteristic roentgenologic pictures develop, with marked changes in the ends of the joint, extensive fractures in the latter, luxations and serious deformations.

The affection may, of course, begin with a fracture in the joint (Figs. 9 a—9 b), but when this is not the case the occurrence of these astonishing changes must be due to the joint-cartilage at places where it has to bear a considerable weight, such as in the knee, the hip or the foot, mechanically getting pounded to pieces as the result of the slight daily traumata to which it is exposed, or perhaps owing to a stamping atactic walk of the patient. As there is complete anesthesia in the joint, no pain is felt, and he continues to walk on the leg with the result that the bone underneath the cartilage gradually is laid bare and, eventually, the spongiosa simply ground to pieces. Small bits of the exposed bone mechanically become torn off and together with the ground-off detritus of bone form larger and smaller free bodies in the joint. As result of the reckless use of the affected member also the joint-capsule and the surrounding muscles are torn to pieces. They react to this with very lively formation of new bone, and together with the loosened periosteum contribute to the formation of the enormous calcareous formations which sometimes end by surrounding the joint as a kind of luxurious callus. If the capsule does not

get torn, it often becomes very much dilated as result of the continued use of the affected joint and the slackness of the muscles; and there then develops the dangling joint which gives the patient what the French call »une jambe de polichinelle».

Fig. 10.

As said, the condition in the joint may develop rapidly, and it is in these cases that the profoundest changes are seen. In other cases the development may take a more chronic course, and when that is the case the osseous tissue gets time to react against the lesions by the formation of osteosclerosis (Fig. 10). The changes around the joint do not become so extensive, and one gets the impression of an eburnation of the joint ends rather than of trituration and fracturing of these.

Just as it is the case with an ordinary callus, the callus-like new formations about the tabetic fractures and changes in the joints for a great part become resorbed when the patient is made to rest and the affection is dealt with on ordinary surgical lines. And it is surprising to see how even a large, sword-like, ossifying myositis may gradually recede almost completely, and how also the severe changes in the joints become softened down (see Fig. 11 a—b and compare with Fig. 6, taken five years earlier).

A typical and very frequent site of the tabetic changes in the joints is in the foot, where we meet the so-called *tabetic flat-foot*. The changes here are of precisely the same character as those in the other joints, and are always a combination of fractures of the tarsals, metatarsals or first phalanges with lesions of the joints; and the picture is so typical that one cannot fail to recognise it when once it has been seen, or when its existence is borne in mind (Fig. 12). The site of the affection is either in the distal row of the tarsal bones — and in that case the bases of the metatarsals are involved — or in the proximal row of the tarsal bones. Owing to the fractures and the resulting severe lesions of the muscles and ligaments of the joints, the arch of the foot collapses, and the picture thus produced is so characteristic that confusion with any other affection is practically impossible. A perforating ulcer of the foot

Fig. 11 a. Fig. 11 b.

often has relation to, and may be conditioned by, an arthropathy in the interphalangeal joints. Fig. 13.

As said, it has been tried in various ways to account for the curious changes in the joints. Many diverse opinions have been advanced, much ink and many printed pages have been expended on the question, and yet no agreement has been reached. The only point on which there has been unanimity is that the changes must in some way or other be connected with the degeneration in the spinal marrow. A few authors, though, have suggested trauma as a contributing factor in the production of the profound changes; among them WILMS, who as the first in 1899 published roentgen pictures of the affection, and WEISZAECKER, who thinks that the fragility of the bones alone is the cause of the arthropathies. Some authors, however, deny this fragility, and, of course, roentgenologically no changes can be seen in the structure of the bones. But though no other authors have confirmed BLANCHARD's and REGNARD's investigations, there is no denying the clinical facts, and to my mind there is no doubt that an osteopsathyrosis, which probably has relation to the degeneration of the spinal marrow, must be considered as a fact. Considering this unquestionable fragility and the whole development of the changes in the joints and their surroundings there can in my opinion, with our present knowledge concerning the pathogenesis of such roentgenologic changes as here observed, be no doubt as to how the picture should be explained.

Fig. 12.

Fig. 13.

As regards the spontaneous fractures there can be no doubt that they are due to the fragility of the bones which notoriously accompanies tabes dorsalis. And the occurrence of the affections in the joints can be explained very simply as due to the same cause. Also the joint-cartilage is a *locus minoris resistentiae*, and the anesthesia which accompanies the disease makes the further development of the arthropathies possible. If this arthropathy does not set in primarily with an actual fracture of the joint, the first clinically demonstrable accumulation in the latter is undoubtedly due to a slight lesion of the joint-cartilage. The patient has no sensation of anything wrong and continues to use the joint; in consequence the injury gradually extends, eventually an actual fracture occurs, and from then on the changes develop in the manner which we know from the roentgenographs. Thus the extremely variegated picture presented by the affection is not a direct manifestation of the patient's tabes, but only an expression for the reaction of the cartilage, the joint-capsule, the bone, the periosteum and the muscles, to the severe lesions resulting from the spontaneous fractures; and the arthropathies are simply a consequence of the fragility of the bone and cartilage, in connexion with the anesthesia — and thus in reality a consequence of the spontaneous fractures.

The roentgenologic picture of the tabetic arthropathies is as a rule so characteristic that the diagnosis is easy. Confusion with tuberculosis or tumor may occur, and even the experienced may, of course, make a mistake. But usually there will be so great difference between both the roentgenologic and the clinical pictures of these diseases that there seldom will be difficulties on this point. Complications with infection, abscess or pyarthrosis may occur, and may to a certain extent obscure

the picture. Where confusion is most often liable to arise is in regard to tabetic arthropathies in the incipient stage in the hip- and knee joints. These may be taken for simple arthritis deformans, especially if the changes show a more chronic course, so that the cartilage and bone get time to react against the lesions by the formation of osteosclerosis and osteophytes. In such cases the roentgenologic picture may very easily be mistaken for that of an arthritis deformans, and may in the earliest stages be impossible to distinguish from it. In the tabetic arthropathies, however, the subchondral cystic formations are lacking, and while it takes years for an arthritis deformans to develop, the development of the tabetic changes is comparatively rapid and soon results in progressive destruction of the joint-cartilage, denudation of the underlying bone, joint-fractures and tendency to subluxation. Therefore it will in doubtful cases soon be possible to establish the right diagnosis. In the case of extra-articular fractures, a very much splintered fracture that causes little or no pain should always make one think of tabes as the possible cause.

SUMMARY

The author reviews the roentgenologic picture of the tabetic arthropathies and spontaneous fractures, illustrates the various forms of the changes and explains the development of the highly variegated picture of the arthropathies. He points out that the diagnosis of tabes dorsalis very often is first established by the relevation of the roentgenologic changes, and that it therefore is of the greatest importance to be familiar with the roentgenologic picture, which for that matter is highly characteristic. He discusses the cause of the occurrence of the changes and expresses the opinion that it in all probability primarily must be the fragility of bones and cartilage accompanying tabes dorsalis, which secondarily results in the great changes around the joint and the bones.

ZUSAMMENFASSUNG

Verf. gibt eine Übersicht des Röntgenbildes der tabetischen Arthropathien und Spontanfrakturen, veranschaulicht die verschiedenen Formen von Veränderungen und beschreibt die Entwicklung des stark wechselnden Bildes des Arthropathien. Er macht darauf aufmerksam, dass die Diagnose der Tabes dorsalis sehr oft erst durch die Entdeckung der röntgenologischen Veränderungen gestellt wird, und dass die Kenntnis des Röntgenbildes, das für diesen Zustand sehr charakteristisch ist, deshalb von aller grösster Bedeutung sein muss. Er bespricht die Ursachen des Auftretens der Veränderungen und spricht die Ansicht aus, dass es aller Wahrscheinlichkeit nach primär die die Tabes dorsalis begleitende Brüchigkeit des Knochens und Knorpels sein muss, die sekundär zu den groben Veränderungen in der Umgebung der Gelenke und Knochen führt.

RÉSUMÉ

L'auteur passe en revue les images radiologiques des arthropathies tabétiques et des fractures spontanées, illustre les diverses formes des modifications et explique le développement de l'image extrêmement variable des arthropathies. Il souligne que le diagnostic

du tabes dorsal n'est souvent posé que sur la constatation des modifications radiologiques et qu'il est par conséquent très important de bien connaître l'image radiographique qui est des plus caractéristiques. Il discute la genèse des modifications et exprime l'opinion que, selon toute probabilité, c'est la fragilité des os et du cartilage accompagnant le tabes dorsal qui est l'élément primaire dont le résultat secondaire est constitué par les modifications profondes des articulations et des os.

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NECROSIS OF THE RENAL PAPILLAE FOLLOWING RETROGRADE PYELOGRAPHY[1]

by

V. Eskelund

Retrograde pyelography is generally considered to be a somewhat disagreeable, but otherwise completely harmless intervention. The contrast media in ordinary use are slightly hypotonic, but as a rule they cause too slight a local irritation and leave the body too quickly to injure the tissue.

The following *case history*, however, seems to bear rather definite evidence of the fact that the intervention in certain circumstances may entail serious impairment of the renal tissue:

A 55-year-old woman had been suffering from dyspepsia, anaemia, and rheumatism for years. She had been hospitalized several times and 3 years prior to the last hospitalization pus and Bacilli coli had been found in the urine. When she was admitted to the hospital in August 1944 she had been febrile and suffering from pyuria for 3 weeks. Treatment with sulfathiazole had resulted in a temporary improvement.

On admission she was not debilitated. The (rectal) temperature ranged from 37° to 38° centigrade. The urine was found to contain a number of leukocytes, but no albumin or renal casts. The blood urea nitrogen was 31 mg. per cent. She was treated with Lucosil (trade name for: 2(p-aminobenzenesulfonamide)methylthiodiazole), $^1/_2$ tablet 6 times daily for 4 days. The coliuria, however, persisted and a treatment with granulatum calcii amygdalati was instituted, but quickly abandoned on account of the violent nausea which it caused. The temperature now rose to 39°—40° centigrade and the treatment with Lucosil was resumed, this time, however, in the form of injections instead of tablets. The dosage was 5 cc. 3—4 times daily. The output of urine was around 1,000 cc. in the 24 hours and the specific gravity nearly constant at 1.002—1.005. The blood urea nitrogen rose to 129 mg. per cent., but again went down to 40 mg. per cent. The temperature also fell to approximately normal values. A new attack was treated with injections of a 40 per cent. solution of Alfasol (trade name for: 2(p-α-sodium ethane sulfonate aminobenzenesulfonamide)thiazole. Sulfanilamide derivative), 5 cc. 4 times daily. Nausea and vomitings, however, persisted and the blood urea nitrogen was somewhat enhanced, viz. 48 mg. per cent.

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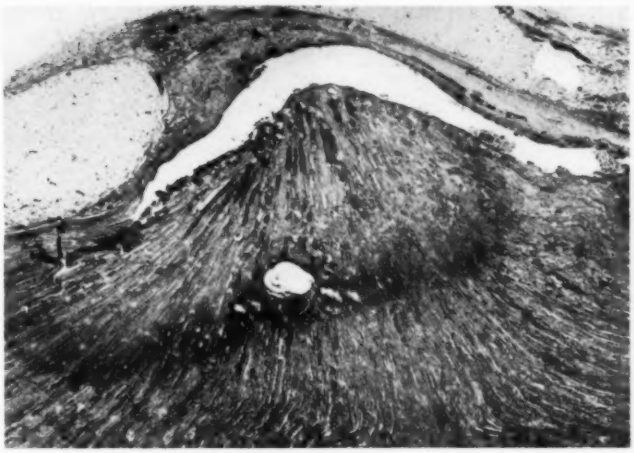

Fig. 1. Necrosis of the renal papillae with dark demarcation area. (× 10)

Since the patient complained of pain in the loins, especially on the right side, and the output of urine was rather low, 500—800 cc. daily, an intravenous urography was contemplated, but in view of the possibility that the impaired function of the kidneys might involve an insufficient excretion of the contrast medium, retrograde pyelography was considered to be more suitable for the purpose. Ureteral catheterization, furthermore, would have the additional advantage of revealing whether or not the passage was unhindered on both sides.

After the insertion of a ureteral catheter and injection of Hippodin (trade name for sodium ortho-iodine hippurate) 25 per cent., 10 cc. into the right and 6 cc. into the left pelvis, a roentgen examination of the urinary tract revealed normal pyelograms and ureters.

The intervention was followed by an even rise in temperature. In the course of one week it rose to values ranging from 38° to 39° where it remained for approximately another week, and afterwards fell evenly to 36° to 37°. Immediately after the intervention the daily output of urine was extremely low, for the first 2 days only 200 and 300 cc. respectively, with a specific gravity of 1.005. During the subsequent period the quantity varied from 200—700 cc. The specific gravity was low too, almost constant between 1.003 and 1.008. With the usual signs of uraemia the blood urea nitrogen rose to 230 mg. per cent. The patient gradually grew weaker until she died in a state of coma less than 1 month after the pyelography. During the last days of life the temperature had been rising and the patient had exhibited signs of pulmonary complications.

Autopsy revealed rather small *kidneys*, 10 × 5 × $3^1/_2$ cm. The capsule could be detached with some difficulty. The surface was somewhat rough with a few, large, rather flat and several small, sharp sunken parts. A few small cysts were also observed. The surface was of a rather motley colour. The projecting portions were light, whereas the sunken parts were somewhat darker, reddish grey. The consistency was slightly flaccid, the tissue rim measured $1^1/_2$—2 cm. and the cortex 3—4 mm. The cut surface was also rather motley and of an almost gelatinous lustre. In several places, especially on a level

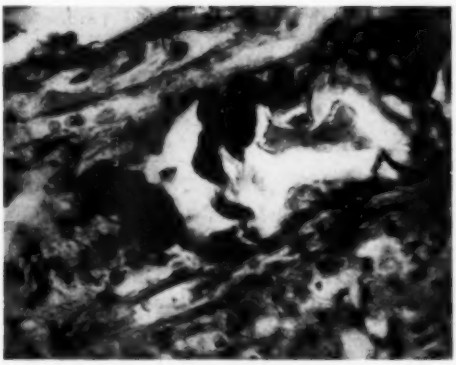

Fig. 2. Microliths in the collecting tubes (× 430). Reprod. 4/5.

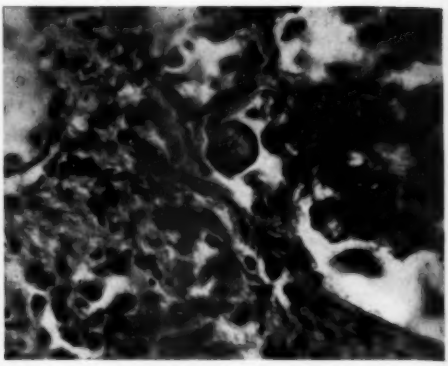

Fig. 3. Microliths in the proximal convoluted tubule (× 430). Reprod. 4/5.

with the sunken portions, the cortico-medullary border was rather vague. The cortex was of a lighter colour than the medulla.

On both sides there was a quite well-demarcated necrosis of all the pyramidal apices which were grey-white, lustreless, dry, and tough, and in certain places almost detached from the base.

The mucosa of the pelvis was marbled with haemorrhagic infiltrates. The pelvis did not contain pus or pus-like fluid, concretions or crystalline precipitates.

Neither ureters nor bladder exhibited grossly visible abnormalities.

The lungs were rather small, oedematous, and hyperaemic. Scattered as well as confluent bronchopneumonias could be seen in the basal area of both lungs.

The remaining organs failed to exhibit changes of interest in this connexion.

Microscopical examination of the renal tissue revealed a complete necrosis of the pyramidal apices as mentioned above. In places the necrotic portions still adhered to the remaining tissue, but in other places they were almost detached. The canals of the necrotic areas contained amorphous and crystalline, rounded bodies with radial stripes and concentric circles. Some of these bodies were clear, others deeply stained with hematoxylin. A number of the canals also contained desquamated epithelial cells in various stages of decay and filamentous structures resembling fibrin. Some of the latter were stainable by Weigert's method, others not. The above-mentioned bodies with stripes and circles were also encountered in one spot on the pyramidal surface. The zone of demarcation was somewhat uneven and hyperaemic. Moreover, the canals of this zone as well as the interstitial tissue exhibited a moderate infiltration by polymorphonuclear leukocytes.

The kidneys contained narrow as well as broad strands and areas with increased connective tissue and infiltration by lymphocytes and plasma cells. In places there were periglomerular fibroses. The same areas revealed some tubular atrophy. Besides these chronic inflammatory changes the acute ones were represented by necrotic areas in cortex as well as medulla with groups of bacteria, necrosis of the surrounding tissue, and a rather moderate infiltration by lymphocytes and polymorphonuclear leukocytes.

Apart from the focal changes described above, the glomeruli were of normal appearance. A few had, however, undergone hyaline degeneration.

In most places the tubular epithelium had become detached and showed signs of post-mortem changes. Several areas of the tubules as well as collecting tubes contained

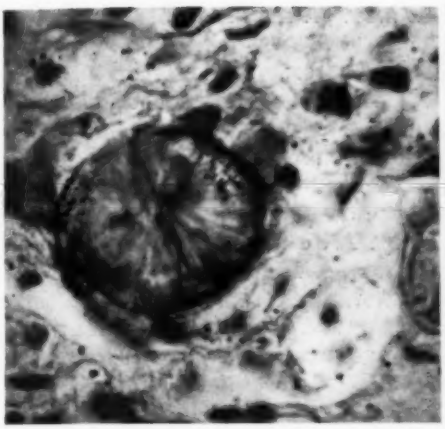

Fig. 4. Microliths in the renal tissue. (× 825). Reprod, 4/5.

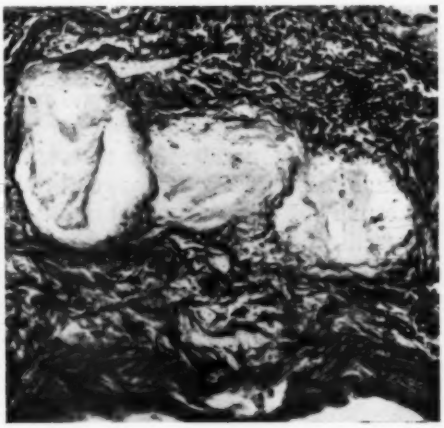

Fig. 5. Thrombi in renal vein. (× 170). Reprod. 4/5.

the »microliths» described above. One of the figures (Fig. 2) presents such a body lying close to a glomerulus in the proximal convoluted tubule. A number of the tubules also contained homogeneous cylindrical casts.

The interstitial tissue was not increased apart from the areas described above. In a few places the tissue had undergone fibrinoid degeneration and was in a state of decay. The fragments stained yellow (van Gieson) and the surrounding tissue revealed a moderate infiltration by lymphocytes.

The renal arteries did not exhibit definite pathological changes, especially no atheromatosis or diffuse hyperplastic sclerosis.

Some of the thin-walled veins close to the pelvis contained thrombotic precipitates (Fig. 5) staining violet with Weigert's fibrin stain.

The mucosa of the pelvis presented marked inflammatory changes. The epithelium had desquamated and the underlying tissue was somewhat thickened and transformed into fibrous tissue, considerably infiltrated by lymphocytes and plasma cells. The blood vessels were hyperaemic. The infiltrations were especially pronounced just below the surface and around the blood vessels. As mentioned above there was only one rounded, crystalline precipitate on the surface.

Discussion

The examination revealed chronic as well as acute pyelonephritis with inflammatory decay and scar-like changes. This finding is in conformity with the anamnesis and the clinical picture and is not an unusual occurrence. The necrosis of the papillae and the crystalline bodies, on the other hand, are extraordinary phenomena.

Neither the acute nor the chronic *pyelonephritis* can have been the direct cause of the necrosis which in that case would be a more common

finding at autopsy. But, as pointed out below, it may have been a contributory or indirect cause.

Other causative factors suggested by the case history might be an impairment of the renal tissue caused by the precipitation of *sulfathiazole crystals* or *the retrograde pyelography*.

On admission to the hospital the patient suffered from pyuria, but the renal function was fairly good at the time. The blood urea nitrogen was normal (31 mg. per cent.) and neither the daily output of urine nor the specific gravity were out of the ordinary. After a period of observation of about 10 days, the patient received a total of 12 g. Lucosil, after which treatment the urine only contained a few leukocytes. The patient now felt well for more than a week, but the pyuria recurred, this time attended with fever. Upon administration of an additional quantity of 10 g. Lucosil the temperature fell and the pyuria subsided, but at the same time the blood urea nitrogen rose to 129 mg. per cent. and did not go down again until more than a week later to 40 mg. per cent. A third attack of pyelonephritis was treated with Alfasol injections, 125 cc. (= 50 g.) in the course of 1 week. When the treatment was terminated the blood urea nitrogen was 48 mg. per cent., the patient was suburaemic with albuminuria and a daily output of urine of about $^3/_4$ litre and a specific gravity of 1.005—1.007. In the course of one month the patient had received 22 g. Lucosil and 50 g. Alfasol. Death did not occur until about 4 weeks after the termination of the treatment which therefore hardly can be considered as the direct cause of death. It may have been the contributory cause of the uraemia, although the autopsy findings do not indicate such a possibility.

In cases of renal injury due to sulfathiazole, the cortex and medulla contain scattered hyaline fragments and strands produced by the decay of the parenchyma around the crystals. The surrounding tissue and the areas in between the fragments contain round cells. Furthermore, there will be hyperaemia and haemorrhages. The epithelium of the kidney pelvis is desquamated and the pelvic surface is sprinkled with rounded, radial, striped bodies, presumably albuminous precipitates around the sulfathiazole crystals, which have been dissolved by the preparation and fixation. In severe cases the pelvis has been moulded by coagulated blood with crystals.

All the reported cases, however, seem to follow an acute course and often lead to death from anuria. The literature accessible for the writer at the moment does not contain descriptions of the injuries after the lapse of a certain period. Presumably the necroses will be followed by fibrous changes. One might think that the albuminous precipitates could become the source of stone formation, but as far as I know, recent years have not brought any striking rise in the number of renal calculi. The precipitates, therefore, presumably dissolve.

The case which I examined contained fibroses which also might have resulted from the pyelonephritis. A few pelvic veins, moreover, contained fibrinous thrombi, a phenomenon which hardly can be said to be specific and may be due to the inflammation. Neither was there an inflammatory oedema of the kidney as presumed by BERGSTRAND. The acute inflammatory changes were localized to the tissue surrounding the groups of bacteria and cannot either be a consequence of the sulfathiazole injury.

The kidneys on the whole did not exhibit changes which could be definitely put down to the sulfathiazole treatment.

The third and only remaining possibility is that the papillary necrosis was caused by the pyelography. The intervention was undertaken at a time when the patient was suburaemic; the daily output of urine was somewhat reduced, there was isosthenuria, albuminuria, and pyuria. During the days immediately following upon the pyelography the output was unusually low and thereupon the temperature rose evenly to 38°—39° centigrade where it remained for about 1 week. It went down again evenly and at the same time the condition of the patient grew worse until she died in a state of uraemia. The temperature again rose during the last days of life, presumably on account of bronchopneumonias. The rise in temperature occurring after the pyelography would not have been so even and so comparatively continuous, if it had been a result of an acute relapse of pyelonephritis.

The contrast medium (Hippodin = sodium ortho-iodine hippurate, 25 per cent.) is hypotonic and causes a slight local irritation, a fact which hardly is of any significance under normal conditions. But in the presence of a reduced output of urine and a general impairment of the renal function the intervention itself presumably may entail a temporary reflex anuria. In case some of the contrast medium has escaped into the papillary ductules an obstruction may result by epithelial necrosis and the accumulation of desquamated cells. If the secretory pressure is reduced, the action is prolonged and the harmful effect increased. In these circumstances an even quite mildly irritating contrast medium no doubt is capable of injuring the renal tissue. The clinical course as well as the fact that the lesion was bilateral and localized to the papillae lend support to this theory. It is not easy, however, to advance a definite proof.

It is difficult to give an explanation of the origin and the significance of the crystalline bodies. Their shape and structure does not correspond to the sediments usually encountered in the urine. Leucine forms rounded crystals, but seldom entails the precipitation of sediments. Leucine, furthermore, is easily soluble in acids and therefore no doubt may be ruled out. Sulfathiazole or similar compounds do not either display this crystalline shape. The same thing may be said of iodine hippuric acid. In a report in Beitr. z. path. Anat. und allg. Path., vol. 86, p. 633 WAXELBAUM mentions

the occurrence of microliths in the renal pelvis of a baby girl, aged 12 weeks, who also exhibited uric acid concretions in the pelvis of both kidneys. Presumably it was a question of albuminuric precipitates around crystals of uric acid which had been dissolved during the preparation. A similar mode of origin may apply to the case under discussion.

All considered, the necrotic changes seem to be explicable as the unusual effect of retrograde pyelography in a patient whose renal function and general condition were extremely poor.

SUMMARY

Bilateral necrosis of the renal papillae was found upon post-mortem examination of a 55-year-old woman who had been suffering from pyelonephritis and died in a state of uraemia. Moreover, the usual signs of acute and chronic pyelonephritis were present and the renal tissue was sprinkled with a number ot »microliths».

Combined with the autopsy findings a review of the case history seems to indicate that retrograde pyelography is the most probable cause of the papillary necrosis. At the time of the pyelography the kidneys were in an extremely bad state — possibly in consequence of chemotherapy — and the intervention was followed by an exacerbation of the condition.

ZUSAMMENFASSUNG

Bilaterale Nekrosen der Nierenpapillen wurden bei der Sektion einer 55-jährigen Frau gefunden, die an Pyelonephritis gelitten hatte und in urämischem Zustande gestorben war. Im übrigen lagen die gewöhnlichen Anzeichen einer akuten und chronischen Pyelonephritis vor, und das Nierengewebe war von einer Anzahl »Mikrolithen» übersäht.

Mit den Sektionsbefunden zusammengestellt, scheint eine Durchsicht der Krankengeschichte nahezulegen, dass retrograde Pyelographie die wahrscheinlichste Ursache der Papillennekrose darstellt. Zur Zeit der Pyelographie waren die Nieren in ausserordentlich schlechtem Zustande — möglicherweise infolge chemotherapie — und auf den Eingriff folgte ein Aufflammen des Krankheitszustandes.

RÉSUMÉ

Description d'un cas de nécrose bilatérale des papilles rénales trouvée à l'autopsie d'une femme de 55 ans atteinte de pyélonéphrite et morte d'urémie. Présence des modifications pathologiques de pyélonéphrite aiguë et chronique avec tissu rénal criblé de microlithes.

Une étude de l'anamnèse dans ses relations avec les lésions trouvées à l'autopsie semble indiquer qu'une pyélographie rétrograde est la cause la plus probable de la nécrose papillaire. Les reins étaient en très mauvais état lors de la pyélographie — peut-être à la suite d'un traitement chimiothérapique — et l'intervention diagnostique a provoqué une aggravation dans l'état de la malade.

FROM THE NORWEGIAN RADIUM HOSPITAL, OSLO (CHIEF: ROLF BULL ENGELSTAD, M. D.)

ON RADIO-SURGERY OF TUMOR METASTASES IN THE LYMPH GLANDS OF THE NECK[1]

by

Rolf Bull Engelstad, M. D.

Lymph gland metastases in the neck have been treated according to highly varying methods during the course of time and at different institutions. Sometimes surgical treatment in the form of more or less radical removal of the affected glandular area has been applied, sometimes radiological treatment, either as external irradiation with roentgen or radium or as interstitial irradiation with intubation of radium needles, transcutaneously or after incision, and sometimes combinations of the two methods have been used.

Prophylactic treatment of the affected gland regions has been widely applied, usually in the form of roentgen or teleradiun irradiation. But prophylactic operation; i. e. prophylactic block dissection of the glands of the neck has also been used to some extent, particularly in carcinoma of the oral cavity.

Among the tumors which metastasize to the lymph glands of the neck, the carcinomata of the lips and the oral cavity are of particular importance, the former because of their marked tendency to cause metastases, the latter because of their high absolute frequency. Metastases are also caused by malignant tumors in the tonsils and the pharynx, carcinomata of the larynx, tumors of the salivary glands, malignant tumors in the nose and its sinuses and occasionally also by malignant tumors of the skin of the head, face and neck. Metastases from a number of other carcinomata, in the glandula thyreoidea, mamma, oesophagus, stomach etc. are of less practical therapeutical significance in this connection. In most of these latter tumor forms the lymph glands of the neck are not the first station for the lymphogenic spreading, and the therapeutic and prognostic problems which arise are therefore of a different nature. In some of the primary or metastatic forms of sarcoma in the lymph glands

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of the neck, lymphosarcoma and reticulosarcoma, special circumstances are significant, primarily the tendency of these diseases to system spreading or system affection.

Topography of the lymph glands of the neck

In the *submental region* there is a group of lymph nodes just about on the midline, corresponding to the raphe m. mylohyoidei (fig. 1). Direct metastases may be found here from cancers in and around the midline in the lips, gums and tip of the tongue.

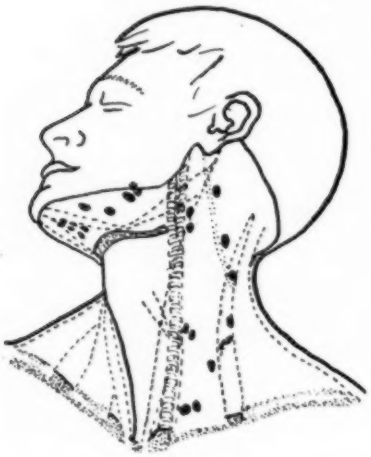

Fig. 1.

In the *submandibular region* there are several lymph nodes, some of them just under the superficial fascia, others deeper in toward the m. mylohyoidei, more or less covered by the salivary gland. There is a lymph node at the art. maxillaris externa which is often the first to be affected.

Along the v. jugularis interna there are two rows of lymph nodes, one lateral to the vein and one in front of it (KÜTTNER, ROUVIÈRE). The lateral row extends from the m. digastricus down to the v. subclavia. About at a level with the m. omohyoideus it swings over from the lateral side of the vein to its posterior side and lies at the lower part of the neck medial to the n. phrenicus on the m. scalenus anterior. The first row consists of three groups of lymph nodes. The upper of these, which is connected with the lateral row, extends from the m. digastricus to somewhat below the bifurcation of the art. carotis communis. The first metastases from tumors in the tonsils and the posterior part of the tongue are often seen here. The middle group is located where the m. omohyoideus crosses the vessel sheath. The first metastases from a cancer of the tip of the tongue may be found as far down as this, carried by a direct lymph vessel. Finally there is the lower group in the fossa supraclavicularis all the way down to the v. subclavia. The lymph vessels from both rows conjoin in the truncus jugularis which empties into the v. subclavia at the angle between the latter and the v. jugularis interna.

In addition to these rows of lymph nodes there are two located more laterally and posteriorly which communicate with each other. The upper of these begins all the way up under the processus mastoideus, behind

the angle of the jaw and below the m. sternocleidomastoideus, where it is connected with the uppermost of the lymph nodes of the jugularis series. It follows the n. accessorius and continues obliquely downwards along the anterior edge of the m. trapezius to the level of the art. cervicalis superficialis. Here it is connected with the second row which is located along the art. cervicalis superficialis and the art. transversa colli almost to the entry of the v. jugularis interna in the v. subclavia. It is important to bear in mind that the most posterior lymph nodes in these series may lie all the way in under the m. trapezius, often 2—3 cm. behind the anterior border of this muscle. In the triangular space which is delimited by the lateral jugularis series and the two last-mentioned series, there are no lymph nodes, but there are of course lymph vessels.

Injection experiments have demonstrated that the different series are connected in a particular manner. When an injection is made in one of the higher, lateral lymph nodes, the injected fluid enters all of the lower lymph nodes except those of the foremost jugular series. If the injection is made in the uppermost lymph node of the foremost jugular series, all of those lying at a lower level are filled except the median group of the same series.

These topographical details, taken largely from ROUVIÈRE, are of the utmost importance both in the clinical examination of lymph node metastases and for their treatment, especially surgical but also radiological.

Diagnosis

In most cases where the presence of metastases in the lymph glands is to be determined, the primary tumor is already diagnosed and the problem is thus considerably simplified. Experience has shown, however, that even under these conditions it may be very difficult clinically to determine whether one or more demonstrably enlarged lymph nodes contain metastases, and at the same time a histological examination may reveal metastases in cases where no enlarged lymph nodes could be palpated. Some examples from the literature will illustrate this.

Carcinoma labii: REGAUD, LACASSAGNE, ROUX-BERGER, COUTARD, MONOD, PIERQUIN and RICHARD in a statistical report from 1927 refer to observations at the Institut du Radium in Paris on lymph gland metastases from carcinoma labii. From 1919—25 a total of 112 cases of this form of tumor were treated. Of 76 patients who were cured, 63 either had or developed enlarged lymph glands of the neck. Only 16 of these were operated affording material for histological examination. In 10 cases there were histologically demonstrable metastases, in 6 cases none.

STANG (1937) found enlarged glands in 13 of 27 patients; their consistency was designated as hard in 4 cases, medium hard in 2 and soft in 7. After operation there were positive histological findings in 2 of the 4 cases with hard glands, negative in 2. The medium hard glands contained no metastases. In the 7 cases with soft glands where roentgen therapy was applied to the neck region, further development revealed that there were metastases in 2 cases.

ASTA BERGENDAHL (1938), in a compilation of Radiumhemmet's material of carcinoma labii, states that extirpation of lymph nodes was performed in 11 cases after radiation therapy. There were metastases in 8 cases while the histological findings were negative in 3.

BULL ENGELSTAD (1939) reports on 11 operated cases, 10 of which had previously been treated radiologically. In the one non-radiated patient there were metastases, as there also were in 8 of the others.

These examples show that the clinical diagnosis of lymph gland metastases is very difficult. This is particularly true when the lymph nodes are only moderately enlarged. The question then arises: How frequently are enlarged lymph glands found in patients with carcinoma labii? Some references to the literature will show that the findings on this point are widely divergent.

KAPLAN found enlarged lymph glands in 10 %, WIDMAN in 25 %, KENNEDY in 60 %, REGAUD and co-workers in 80 % and STANG in about 50 %. ASTA BERGENDAHL found no, or only soft, non-suspicious glands in 159 cases, suspicious or definitely cancerous in 60 cases which were operable, and inoperable glands in 6 cases. In BULL ENGELSTAD's material 46 had no demonstrably enlarged lymph glands, 40 had enlarged but non suspicious and 60 had suspicious or definitely cancerous glands.

Carcinoma oris: In connection with various carcinomata in the oral cavity (in the tongue, floor of the mouth, gums, cheeks and palate) enlarged lymph glands are often encountered but not all of them contain metastases.

REGAUD and co-workers (1927) report on a material of 311 patients with carcinoma of the tongue or the floor of the mouth. Of these there were only about 25 % who did not have or develop spreading to the lymph glands. Operation was performed on 23 patients with swollen lymph glands: the histological examination revealed metastases in 12, none in 11.

BERVEN (1932) in a material of 64 tongue cancers from 1916—1921 found gland metastases in 39 %, no metastases in 61 %. In a material of 50 patients from 1922—26 the corresponding figures were 46 % and 54 %. In another publication BERVEN mentions the possibility of incorrect diagnosis and emphasizes that this may take place in both directions. In the material from Radiumhemmet the most frequent incorrect

diagnosis seems to be that clinically cancer suspect glands turn out to be the site of inflammatory processes.

DAHL (1934) claims that histological examination of the small, soft, non-suspicious glands reveals metastases in about half of them and that incorrect diagnosis in the opposite direction is just as frequent.

BULL ENGELSTAD (1938) in a material of 135 patients with carcinoma of the oral cavity found that no gland metastases could be demonstrated in 52 cases over an observation period of from 3—5 years, while 83 developed metastases sooner or later. Of these latter only 63 were in such condition that treatment could be administered. In 19 cases block dissection of the glands was performed after teleradium treatment; the histological examination revealed that there were metastases in 16 cases while there was no tumor tissue in the other 3. Metastases were demonstrated in both of 2 cases operated without previous radiation therapy.

Personal investigations: In the years 1932—1944 a total of *601* patients has been treated at The Norwegian Radium Hospital for *carcinoma labii*. The first examination revealed no palpable lymph nodes in *200* cases, small in *339* cases and not or only slightly suspicious of cancer, in *62* cases there were firm or hard lymph nodes which were interpreted as cancerous. We shall not take up space here with a detailed analysis of this entire material but shall discuss only those patients on whom removal or block dissection of the glands has been performed so that the clinical diagnosis is verified.

Operation has been performed on 39 patients. In 3 cases the clinical diagnosis was uncertain and the glands were removed for diagnostic purposes. There were metastases in all 3 of these cases. All had previously been treated radiologically; in one of the cases the tumor tissue in the extirpated gland showed marked irradiation changes.

In 7 patients, all of whom had previously been treated radiologically as metastases had been clinically diagnosed, block dissection of the upper glands of the neck was performed. In 6 cases the diagnosis was confirmed by the histological examination; in one of these cases there was a marked radiation effect on the tumor tissue. In one patient where the clinical diagnosis was submandibular gland metastases the histological examination revealed only a radiologically altered glandula submandibularis.

Of 29 patients with clinically diagnosed metastases where total block dissection of the neck glands was performed, 27 had previously been treated radiologically and 2 not. In one of the 2 latter there were metastases while the other had a sinus catarrh. Among the others, 20 had metastases, 2 with very pronounced radiological alterations, while there was no tumor tissue in 7. In these cases the histological diagnoses were: Lymph node with reactive alterations or chronic adenitis in 3 cases,

tuberculosis in 2 cases and radiologically affected salivary gland in 2 cases. In one of these last mentioned, block dissection of the upper glands of the neck had been performed on the other side and metastases were found histologically.

Our material of *carcinoma oris* for the years 1932—1944 consists of 588 patients. In *173* the first examination revealed no, in *320* small, slightly or non-suspect lymph nodes, while *95* had glands which were interpreted clinically as metastases.

In 56 of the patients the glands were removed surgically after the clinical examination had revealed definite or suspect metastases. In 4 cases only an upper block dissection was performed ad modum RAYMOND BERNARD; all 4 had previously been treated radiologically. In 2 of these the cancer diagnosis was considered certain, in the other 2 more doubtful. The histological examination revealed metastases in all 4, but in one there were very pronounced irradiation changes.

In 52 patients, 44 of which had been previously treated radiologically, total block dissection of the neck glands was performed ad modum ROUX-BERGER. In 41 of these cases the histological examination revealed metastases, of which 8 showed strong indications of irradiation effect. In 11 cases there was no cancer and 2 of these, not previously treated radiologically, had clinical symptoms of definite metastases. In one of these the glandula submandibularis showed pronounced radiological alterations (a result of irradiation of the primary tumor), in the other there were lymph nodes with reticulum cell reaction.

In addition to the above-mentioned carcinomata of the lips and the oral cavity, block dissection of the neck glands has been performed in connection with a number of other tumor forms: *carcinoma tonsillae:* 2, *reticulosarcoma epipharyngis:* 1, *carcinoma hypopharyngis:* 1, *carcinoma laryngis:* 4, *malignant tumor on the glandula submandibularis:* 2, *»tumor colli»:* 3, *malignant tumor in the nose or sinuses:* 3, *tumor parotidis:* 2, *carcinoma cutis:* 2 and *melanoma malignum* or *nævus cell tumor:* 3.

In one of the patients with carcinoma tonsillae who had previously been treated with roentgen, the histological examination revealed tuberculous lymph nodes and no indications of metastases.

In 2 previously radiologically treated patients with carcinoma laryngis no metastases were found: there were lymph nodes with reactive alterations in the one case, a radiologically altered salivary gland in the other.

One of the patients with »tumor colli» gave the clinical appearance of a malignant tumor. When block dissection of the glands was performed after radiological therapy the only findings were indications of a chronic specific inflammation, tuberculous or syphilitic. The 2 other patients with »tumor colli» were found on histological examination to have reti-

culosarcoma in one case and carcinoma metastasis — with no demonstrable point of origin — in the other.

This last group of various kinds of tumors includes a total of 23 cases where lymph node metastases or primary tumors in the lymph nodes were diagnosed clinically; the diagnosis was verified histologically in 19 cases, while no tumor tissue was found in the extirpated glands in 4 patients. There were pronounced radiological alterations in 7 cases.

The compiled material presented here consists of 118 patients in whom lymph node metastases were diagnosed clinically; however in 3 of these cases the clinical diagnosis was uncertain. *The clinical diagnosis was verified histologically in 94 cases* (*79.7* %), *while in 24 cases* (*20.3* %) *no metastases were found*. Very pronounced radiological alterations in the metastases were found in 20 patients (17.2 %).

The pathological alterations found in those cases where there were no metastases were: reactive alterations, sinus catarrh and chronic inflammation (tuberculosis, syphilis). In some cases an enlarged and radiologically altered glandula submandibularis was incorrectly interpreted as a submandibular lymph node metastasis.

The frequency of incorrect diagnosis in the opposite direction, or in other words the overlooking of metastases, cannot be judged on the basis of our material. It is true that there were metastases in some cases which were not demonstrated at the first examination, but there is no way of determining whether these were already present at the time of the first investigation or whether they developed later. The chronological development in these cases cannot be definitely determined.

We shall therefore not go further into this question but only mention as an example that in a material of 153 cases of carcinoma linguae no cancerous or cancer suspect glands were found in 115 (75.2 %) on the first examination. Of these 115, 33 (28.7 %) later developed gland metastases. These comprise 21.6 % of the entire material so that in all there were metastases in 46.4 % of the total. As all of the patients were not control examined by us during the entire course of the disease, the possibility cannot be eliminated that the figure actually is still higher.

The diagnosis of lymph node metastases may be easy, especially in well developed cases. Where the tumor infiltration has penetrated the capsule the glands become adherent to each other and their surroundings, there is a diffusely limited hard infiltration and there may also be symptoms from vessels or nerves which are subject to pressure or infiltration: congestion, edema, radiating pains, Horner's syndrome. In the early cases the size and consistency of the glands will form the basis of the diagnosis. A hard gland of hazel nut size or larger will in most cases, but not always, prove to be a metastasis. However if there are one or two small, pea or bean sized firm glands the diagnosis may be difficult,

even for an experienced investigator. In these cases only a histological examination can provide a reliable diagnosis.

Therapy

At most of the radiological therapeutical clinics outside of France lymph node metastases of the neck have been treated primarily radiologically, usually either with roentgen or teleradium (BERVEN, DAHL, BULL ENGELSTAD). The further procedure has varied somewhat. Either the patient has been kept under careful control and operated only in cases where there were clinical indications that the metastases were not destroyed or operation has been performed regardless of the clinical findings after radiological therapy. Radium intubation in conclusion to the operation has been applied by some, but more frequently post-operative radiological therapy with roentgen or teleradium has been applied.

One form or another of radiological or combined surgical-radiological treatment has been used at most clinics for the various kinds of tumors which may be involved in these cases. However a different standpoint is taken at the Institut du Radium in Paris, especially concerning the treatment of carcinoma of the oral cavity. REGAUD and co-workers (1927) and ROUX-BERGER and TAILHEFER (1933) strongly emphasize the significance of a total block dissection of the neck glands on the affected side immediately after radium treatment of the primary tumor. The other side is not operated unless the primary tumor extends beyond the median line. Block dissection of the glands is performed regardless of whether there are palpable glands or not. Postoperative radiological treatment was earlier administered if cancer was demonstrated histologically, but in more recent years this has been dropped and is reserved for eventual relapses.

At The Norwegian Radium Hospital the treatment of metastases of the glands of the neck has in general been carried out according to the following principles: In carcinoma labii the local gland region is not treated unless there are palpable, suspect glands. When these are present radiological treatment is administered first, usually teleradium, and its effect is awaited for 6—8 weeks, after which a block dissection of the glands of the neck is performed when necessary. In carcinoma of the oral cavity the nearest regional lymph areas are always treated at the same time as the primary tumor; otherwise the treatment is carried out according to the same principles as for carcinoma labii. In tumors of the salivary glands, sinus carcinoma and carcinoma of the vocal cords as well as carcinoma cutis the local gland regions are usually not treated simultaneously with the primary tumor, but in the other tumor forms included in this material the entire adjacent lymph region is irradiated

usually on both sides. In these various tumor forms operation is usually not performed unless the radiological treatment proves to be without result.

In recent years we have applied primary surgical treatment in some cases with post-operative teleradium or roentgen irradiation, especially in carcinoma of the oral cavity in relatively young patients.

Now we practically always perform a total block dissection of the neck glands. Upper block dissection of the neck glands was previously used to some extent, especially in carcinoma of the lips, but is now only used exceptionally in old and debile patients. Gland extirpation is employed practically exclusively for diagnostic purposes where the clinical diagnosis does not afford sufficient certainty.

The operational method employed is derived from CRILE and MORESTIN (1910) and has been further developed by ROUX-BERGER and his co-workers. The object of this operation is to remove the entire tissue area where the lymph glands and vessels of the neck are located in one piece, »en vase clos».

An incision is made along the posterior border of m. sternocleidomastoideus along its entire length. From about the middle of this incision another is made toward the submental region to just above the other side of the chin. The skin patches, with or without platysma, are then dissected aside forward to the median line, up to the mandibular edge, down to the clavicula and back to the anterior trapezius edge. Just above the clavicula the superficial fascia and the m. sternocleidomastoideus are cut through, then the fascia colli media in to the v. jugularis interna which is doubly ligatured and then cut. Contact is then sought with the muscular limitations and with the most important vessels and nerves. Fatty tissue and glands from the fossa supraclavicularis are then removed as far as is possible; on the left side the ductus thoracicus must be borne in mind.

The dissection is then made from below and upward, extending forward to the median line and backward to the anterior border of the trapezius and somewhat under the latter. Inward to the art. carotis and n. vagus as well as the m. scalenus ant. and the other deep muscles of the throat, removing adventitiae and perimysiae. The v. jugularis int. is always taken when only one side is operated as this facilitates the operation considerably. When a bilateral operation is performed the vena jugularis should be left intact on one side and should then be dissected free of its adventitia. Deaths have been reported after bilateral resection of the vein, but on the other hand cases have also been reported where the vein had to be sacrified on both sides and results have been good.

At a level with the bifurcation of the art. carotis contact is sought

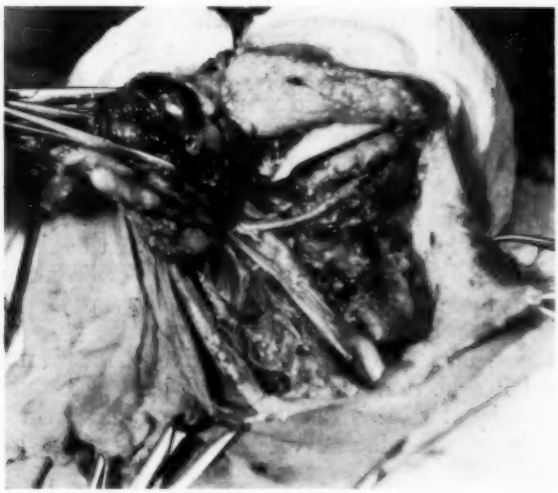

Fig. 2.

with the os hyoideum, m. digastricus, m. stylohyoideus and n. hypoglossus. Recently we have included the posterior part of the digastricus and the m. stylohyoideus as do ROUX-BERGER and TAILHEFER, which facilitates the dissection of the region under and behind the angulus mandibulae. In submandibular dissection, which we always perform from the front backwards, we go in under the perimysium of the m. mylohyoideus, if necessary remove some of the periosteum on the mandible if there are adherent glands, and always remove the glandula submandibularis (fig. 2). On continuing backward until the upper end of the m. sternocleidomastoideus is cut through, the piece to be removed is attached only by v. jugularis int. This is finally ligatured as high as possible and the entire freely dissected block can then be removed.

The loss of the m. sternocleidomastoideus causes no functional disturbance. Severing of the n. accessorius, which cannot be avoided, leads to atrophy of the m. trapezius but this is of little significance. If the circumstances are such that it is impossible to avoid severing the sympaticus or the n. phrenicus, the results are not serious. Even severing of the n. vagus makes little difference but may lead to temporary hoarseness. Irritation of the n. vagus by pulling or pressure may be more serious. The n. hypoglossus can usually be avoided without difficulty but even if it has to be sacrified on one side this is not serious. The art. carotis communis can usually readily be dissected free; where it is necessary to ligature this artery the consequences may be catastrophic, hemiplegia

or mors. The art. carotis int. must also be avoided, but in some cases we have found it necessary to ligature the art. carotis ext. without any detectable consequences, but such were not to be expected either.

In performing the upper block dissection of the neck glands ad modum Raymond Bernard the operation is limited to the area above the m. omohyoideus, and the m. sternocleidomastoideus, v. jugularis int. and n. accessorius are spared.

Block dissection of the glands of the neck is performed under a paravertebral anæsthetic according to the method of COQUELET (1930). The canula is inserted at the tip of the proc. mastoideus directed toward the transverse process of the 6th cervical vertebra. It is then easy to find the transverse process of the 3rd cervical vertebra which is at the same level as the upper border of the cartilago thyreoidea and an abundant quantity of the anæsthetic is placed here and on the transverse process of the vertebra below. This assures anæsthesia of the anterior and lateral sides of the neck. If additional infiltration anæsthetic is administered along the edge of the jaw, behind the angle of the jaw, along the edge of the trapezius and in the regio submentalis at the median line, the anæsthesia is complete. Scopolamine-morphine or scophedal should be administered first.

Results: The material presented here includes all the surgically treated cases of lymph node metastases at the Norwegian Radium Hospital in the period 1932—1944, in all 118 patients.

Simple *extirpation of lymph node metastases* has, as mentioned above, been used chiefly for diagnostic purposes and has been carried out in 3 cases of carcinoma labii. There were metastases in all 3. One patient was symptom free for nine years when he died of pneumonia, after having been treated for carcinoma recti in the interval with good results. The 2 others both died of cancer after $1\,^1/_2$ years.

Upper block dissection of the neck glands has been employed in 7 cases of carcinoma labii and 4 cases of carcinoma oris, in all 11 cases.

The results are presented in Table 1.

Table 1.

Upper block dissection of the neck glands.

	Total	No recidivation			Died of ca.		
		< 3 yrs.	> 3 yrs.	> 5 yrs.	Total	No gland rec.	Gland rec.
Ca. labii	7	1	1*	2	3	1	2
Ca. oris	4	1			3	3	

* Died of pneumonia after $4^1/_2$ years.

There was no operation mortality in this group. Of the patients who died of their carcinoma labii 2 developed gland recidivation on the operated side while 1 died of other metastases. The length of life for these patients was from 1 to 3 years. Of the patients with carcinoma oris none developed gland recidivation; 2 died as a result of the progression of the primary tumor, one developed a cerebral affection which was interpreted as probably due to tumor metastases. The length of life for all 3 was about 1 year.

In Table 2 the results of all the total block dissections of the neck glands which we have performed are compiled. The operation has been performed on a total of 104 persons: 44 times on the right side, 51 on the left and 9 times bilaterally; the bilateral operation is always performed in 2 sessions at varying intervals. Thus 113 total block dissections of the neck glands have been performed on these 104 patients.

Even though this operation is extensive, it has been tolerated surprisingly well in spite of the fact that most of the patients were well on in years, some of them very old. The operation mortality is very low. A 75 year old woman, who was already quite debile, developed hemiplegia 4—5 days after the operation on the operated side and died 3 weeks later (previously reported by DAHL). A 60 year old man was operated in spite of the fact that operability was regarded as very doubtful. During the operation metastases were found deep in the fossa supraclavicularis and in attempting to loosen these there was severe hemorrhage which was controlled with difficulty; the operation was carried out although not radically but the patient did not recover and died shortly afterwards. In a 77 year old man an extensive electro-coagulation of a tongue cancer was first performed under evipan-sodium anæsthetic and a few days later a total block dissection of the neck glands. A few days after the operation there were signs of heart failure which led to death in the course of a few days. Finally in a 56 year old man a block dissection was performed first and later an electro-coagulation of a large recidivation at the root of the tongue under evipan-sodium anæsthetic; here a fatal bronchopneumonia developed.

We have thus 4 post-operative deaths (3.5 % of 113 operations), but in 2 of these other severe operations were performed in the form of extensive electro-coagulations. Only 2 of the patients on whom block dissection of the neck glands was performed with no accompanying operation died in conclusion to the operation which gives an *operation mortality of 1.8* %. Moreover the operation mortality is naturally dependent on the indications followed, the age and general condition of the patient, the size of the gland metastases, their extent and relation to their surroundings. Based on reasonably cautious indications the operation risk is undoubtedly very small, practically nothing.

For comparison it may be mentioned that ROUX-BERGER and TAILHEFER (1933) have 6 deaths after 212 operations; with the more conservative indicational basis they now use they reckon with no operation mortality. SANDBERG (1945) has performed 39 total block dissections of the neck glands on 37 patients with an operation mortality of 2.7 %.

The 4 patients mentioned above are recorded in Table 2 and the following as having died of their cancers.

Table 2.

	Total	Rec. free			Rec. free died of other causes	Alive with rec.	Died of cancer		
		< 3 yrs.	> 3 yrs.	> 5 yrs.			Total	No gl. rec.	With gl. rec.
Ca. labii	29	3	3	15	2	1	5	3	2
Ca. oris	52	5	4	9	5		29	20	9
Ca. tonsillae	2						2	2	
Reticulosarc. epipharyngis	1					1			
Ca. hypopharyngis	1						1	1	
Ca. laryngis	4			1	1		2	2	
Salivary gland tumors (parotis, gl. submand.)	4			1			3	1	2
»Tumor colli«	3			1			2		2
Ca. cavit. nasi et sinuum	3						3	3	
Ca. cutis	2						2	1	1
Melanoma malign., mal. nævus cell tumor.	3	1			1		1	1	
Total	104	9	7	27	9	2	50	34	16
		43						50	

Of the entire material of 104 patients there are at present 43 (41.3 %) who are alive and free from recidivation, 50 (48.1 %) have died of their cancers, 2 are alive with recidivation while 9 have died of other intercurrent diseases without developing recidivation of their malignant tumors. We shall briefly review the causes of death of these 9 patients.

Four of the patients later developed other malignant tumors, as 3 of them (1 lip, 1 mouth and 1 hypopharynx cancer) died of carcinoma oesophagi after $2\,^1/_2$, 1 and more than 3 years respectively, while the 4th (ca. oris) died of carcinoma ventriculi with ascites after 4 years without recidivation. In all of these patients the cause of death was undoubtedly a new primary tumor having no direct connection with the one previously treated. The coincidence of several independent primary cancers in the upper part of the digestive tract is no rarity; in this connection I can refer to a report from The Norwegian Radium Hospital by A. SCHEEL.

Two patients died of bronchopneumonia, one (ca. labii) after $10\,^1/_2$ years without recidivation, the other (ca. palati) after $1\,^1/_2$ years. One patient (ca. linguae) died of vitium cordis after 10 years without recidi-

vation and one of hemorrhagia cerebri after 4 years. The last of the patients in this group (ca. linguae) died suddenly of unknown cause, possibly of hemorrhagia cerebri, 2 years after bilateral total block dissection of the neck glands. He was controlled at The Radium Hospital a short time before his death and exhibited no symptoms of local recidivation, gland or other metastases.

The two patients alive with recidivation are one with ca. labii, one with reticulosarcoma epipharyngis. In the former a block dissection of the neck glands was performed on the right side almost 3 years ago; he now has a diffuse, hard infiltration on the operated side and extensive, inoperable gland metastases on the other side. It should be added that this patient, who lives at a considerable distance from the hospital, has neglected the regular control examinations. The other patient was treated with roentgen in 1942 for reticulosarcoma in the epipharynx with lymph gland metastases. After about $1^1/_2$ years without recidivation, rapidly growing metastases appeared on both sides of the neck. A year ago block dissection of the neck glands was performed on the right side and the intention was to perform the same on the other side but the patient refused. Moreover the metastases on this side were by this time of doubtful operability. At the last control examination there was considerable progression of the metastases on the left side; on the operated side there was no gland recidivation but there was a small cutaneous nodule just at the scar, possibly an implantation metastasis.

For 9 of the 43 patients now alive without recidivation the period of observation is less than 3 years; they will therefore not be discussed in more detail. For the rest of the patients without recidivation the results are compiled in Table 3. In the 3 and 5 year statistics respectively those patients are included where the operation was performed 3 and 5 or more years ago and the results include all of the patients who were symptom free 3 and 5 years after the operation; 4 of the patients who were symptom free for 3 years, and of these 2 who were also symptom free after 5 years, died later of intercurrent diseases and are already accounted for.

Table 3.

	3 years		5 years	
	Total	Symptom free	Total	Symptom free
Ca. labii	23	19 (82.6 %)	20	16 (80 %)
Ca. oris	39	15 (38.5 %)	30	10 (33.3 %)
Other tumors	14	5 (35.7 %)	8	3 (37.5 %)
All tumors	76	39 (51.3 %)	58	29 (50 %)

The figures within each group are too small to allow of any statistical treatment; nevertheless the percentile freedom from symptoms is recorded merely to give a clearer impression of the results obtained. As is to be expected the results for *carcinoma labii* are much better than for the other tumor forms: *82.6 % symptom free after 3 years and 80 % after 5 years.* In *carcinoma oris* we find *38.5 % after 3 years and 33.3 % after 5 years,* in the *other tumors 35,7 % after 3 years and 37.5 % after 5 years.* That the results in the last group are better after 5 years than after 3 is due to purely chance circumstances which arise in this small material.

The results in all the groups are surprisingly good, better than the average for all the treated cases within the single groups and this requires closer explanation. It is obvious that the results obtained in a material like the present are extremely dependent on the indications followed. If block dissection of the neck glands is performed where the possibility for a radical operation is slight or doubtful, or if the operation is performed even in cases where the chances for controlling the primary tumor are small, the end results will necessarily be poor. That our results are so good is undoubtedly due to the fact that we have on the whole held to very strict limitations concerning the indications for operation: *we have generally not performed block dissection of the neck glands unless we believed that we could also check the primary tumor, and we have also usually required that there was a high probability that the operation could be carried out radically.* It is difficult to evaluate the significance of the fact that most of our patients were given radiological treatment of the local gland region beforehand, and some of them also had post-operative treatment, but it must be permissible to assume that this treatment has been of considerable importance, as most of the tumors concerned here are readily susceptible to irradiation. The histological examinations have also showed that in many cases the effect of the radiological treatment has been marked.

Under any circumstances it is justifiable to conclude from our material, which on the *whole shows a 3 years' freedom from symptoms in 51.3 % and a 5 years' freedom from symptoms in 50 %*, that total block dissection of the neck glands is a valuable help in the treatment of these tumors. This appears even more clearly when the purely local results are considered, in other words the freedom from symptoms or the recidivation frequency within the operated lymph system area.

However we shall first review the *causes of death* in the cases where the patients have died from — or with — their malignant tumors (Table 4).

It appears from this table that in most cases it is either progression of the primary tumor or distant metastases which have been the cause of death, while in only about $^1/_3$ of the cases has recidivation or progression

Table 4.

	Total	Progr. of primary tumor	Rec. or progr. of gland metastases	Distant metastases
Ca. labii	5	2	2	1
Ca. oris	29	12	9	8
Other tumors ...	16	5	5	6
All tumors	50	19	16	15

of the lymph node metastases been the cause of death. It has been found especially in carcinoma oris that the primary tumor is difficult to check, a circumstance which should be ascribed significance when considering the indications for total block dissection of the neck glands.

The length of life for these 50 patients has been over 3 years in 7 cases only, the other 43 patients died within 3 years, most of them 1—2 years after operation.

Finally, if we consider the *local results* of the block dissections performed, in other words the recidivation frequency within the regional lymph system on the operated side, it appears from Table 2 that of the 50 patients who died of — or with — their malignant tumors, there were only 16 who at death had demonstrable lymph node metastases. Among these are also included the patients who were free of recidivation on the operated side but had lymph node metastases on the other side. There were 3 such cases. However the fact that 2 patients with recidivation are alive must also be considered, in both cases with lymph node metastases on both sides of the neck, so that the sum of the patients with recidivation or progression of lymph node metastases on the operated side will be 15.

In a material of 104 patients with 113 total block dissections of the neck glands, recidivation has developed in 15 cases while 89 patients showed no recidivation — nor new metastases — on the operated side during the observation period.

The local results of the operation after 3 years' observation are presented in Table 5, where all patients in the material who have been controlled over this period are included. Of the patients with carcinoma labii 2 died with gland recidivation and 1 is alive with recidivation; all 3 were operated more than 3 years ago. Of the 9 patients with carcinoma oris who died with gland metastases only 7 had recidivation on the operated side. The time elapsed since the operation is more than 3 years for 5 of them. In the group with other tumors 5 died with gland metastases, of which 4 on the operated side. Moreover 1 patient with gland recidivation is still alive. Of 5 patients who have recidivation on the operated side, the operation in 3 cases was performed more than 3 years ago.

Table 5. *3 years.*

	Total	Without recidivation on the operated side
Ca. labii	23	20 (87 %)
Ca. oris	39	34 (87.2 %)
Other tumors	14	11 (78.6 %)
All tumors	76	65 (85.5 %)

Briefly summarizing the results of the regional effect we see that *of all 104 patients only 15 (14.4 %) developed gland recidivation on the operated side.* Among the *76* patients who were operated *3 or more years* ago, there was recidivation in *11 cases (14.5 %).*

These figures obviously are not an exact expression of the effect of the method as we do not know how many gland recidivations might have developed in those patients who died during the observation period as a result of progression of the primary tumor or of distant metastases, nor are those cases regarded as inoperable included in the compilation. However the results presented in Table 5 and in the preceding tables show clearly that total block dissection of the glands of the neck can be performed in a very large number of operable cases as a radical operation for this region, and in this manner it is possible to check regional metastases to a great extent. However, at the same time it should be emphasized that most of the patients in this material were treated radiologically beforehand and some of them also post-operatively. The significance of this treatment should not be undervalued.

Indications: We have considered the question as to whether we should apply prophylactic block dissection of the neck glands on the affected side more extensively, at least in cases of carcinoma oris, as has long been the practice at the Institut du Radium in Paris. However we find no reason to change our practice radically, but believe that primary, and in some cases prophylactic, block dissection of the neck glands should be performed more often than hitherto, among other reasons because of the difficulty of the clinical diagnosis of lymph node metastases.

In cases of *carcinoma labii* it is usually possible to check the primary tumor. As the tendency to metastases is generally relatively moderate in these cases the local lymph region is not treated unless cancer suspect glands are found. When the latter is the case, primary radiological treatment is usually administered and block dissection is performed only when the glands do not respond completely to the radiological treatment. The prerequisite for this procedure is that the patient must be kept under frequent, careful and specialized control. If these requirements cannot be

fulfilled it is reasonable to apply primary surgical treatment with post-operative roentgen or teleradium treatment. The same is true of rapidly growing metastases, especially in relatively young patients where the operation usually does not involve any risk. Prophylactic block dissection is seldom indicated in this form of tumor.

As regards *carcinoma oris* some of the same considerations hold good but here regard must be taken of the considerably greater tendency to spreading and the fact that the primary tumor is often difficult to check. The adjacent glandular region is always included in the irradiation of the primary tumor and if there are cancer suspect glands the entire neck region is irradiated. When the radiation reaction to the primary treatment has subsided, it is possible to make a decision as to the advisability of block dissection; it will then also be easier to form an opinion as to the possibility of checking the primary tumor. If there are palpable, cancer suspect glands at this time, a total block dissection of the neck glands should be performed according to our present knowledge, on condition that the primary tumor has disappeared or is regarded as curable with continued treatment. Under these last conditions there may also be reason to apply prophylactic block dissection much more extensively than we have hitherto done. This should be actual especially if the geographical conditions or other circumstances make it difficult to maintain regular and effective control. It would also be correct to apply this procedure especially in relatively young patients.

However, we see no reason to perform prophylactic block dissection of the neck glands systematically in all cases of carcinoma oris; if there is no reasonable chance that the primary tumor is curable the patient should usually be spared this extensive operation. However there may be exceptions, for example cases where there are rapidly growing lymph gland metastases and where palliative considerations afford the indications to remove them regardless of the chances for a radical cure.

Post-operative radiological treatment after block dissection of the neck glands should be the rule in our opinion, unless such large doses have been given previously that it must be omitted for this reason.

The indications for block dissection of the neck glands should in our opinion not be confined to a schematic, routine program, but should be highly individualized, taking consideration of all of the circumstances mentioned in the preceding.

Also in the heterogenous group of *other tumors* included in this material, the treatment of lymph node metastases, and thus also the indications for block dissection of the neck glands, should be highly individualized. In some of these tumor forms, such as tumors in the tonsils and epi-, meso- and hypopharynx, the entire neck region is always irradiated on both sides, as well as cases of primary tumors in the lymph

nodes of the neck. In carcinoma of the vocal cords, salivary gland tumors and sinus tumors the tendency to metastases is so slight that it may be regarded as defensible to wait with treatment of the lymphatic region as long as the patient is kept under careful control. In carcinoma cutis lymph node metastases are a rarity and treatment of the regional lymphatic system comes into consideration only exceptionally. It is difficult to give definite directions for malignant melanomata and malignant nævus cell tumors; here the treatment is dependent on the histological findings in the primary tumor, its localization and accessibility for radiological and surgical treatment. Primary or prophylactic radiological therapy of the local gland regions is usually indicated, early block dissection of the neck glands, eventually prophylactic, may be.

In all of the tumor types discussed here, an intractable primary tumor or demonstrated distant metastases contra-indicate a total block dissection of the neck glands; however in exceptional cases palliative considerations may make a more or less radical operation on the gland metastases desirable. Advanced age, poor general condition or the presence of other diseases may here, as in other surgical cases, naturally comprise contra-indications.

The radical operability of lymph node metastases must always be considered very carefully beforehand; if the clinical examination does not make it seem probable that the operation can be performed radically, radiological treatment should be administerd first in our opinion; further observation of the patient will then show whether a subsequent block dissection of the neck glands is necessary and feasible.

SUMMARY

After a short description of the topography of the lymph nodes of the neck an account is given of the difficulties of the clinical diagnosis and the frequent discordance between the clinical and the histological findings. In the present material of 118 patients (carcinoma of the lips, the oral cavity and a number of other tumors) the clinical diagnosis was verified by the histological examination in 79.7 % while in 20.3 % there were no metastases. Most of the patients had been treated radiologically beforehand; in 17.2 % very pronounced irradiation effect was found.

An account is then given of the surgical treatment applied. Total block dissection of the neck glands (ad modum ROUX-BERGER) has been performed on 104 patients, of which 9 bilaterally, in all 113 total block dissections with an operation mortality of 1.8 %. On a more conservative indicational basis the author believes that operation mortality could be practically eliminated. Of the 104 patients 41.3 % are at present free from symptoms 48.1 % have died of cancer (observation period 1—12 years).

The results after 3 and 5 years' observation time respectively are: in carcinoma labii 82.6 % and 80 %, in carcinoma oris 38.5 % and 33.3 %, in the other tumors 35.7 % and 37.5 % and for the total material 51.3 % and 50 % free from symptoms. In all 50 patients have died from, or with, their malignant tumors. In 19 cases death was due to progression of the primary tumor, in 16 cases to recidivation or progression of gland

metastases and in 15 cases to distant metastases. Freedom from symptoms in the operated local gland region after 3 years: in carcinoma labii 87 %, carcinoma oris 87.2 %, other tumors 78.6 %, and in the entire material 85.5 %. The significance of preceding or subsequent radiological treatment is emphasized.

Finally the indications for total block dissection of the neck glands are considered in the various tumor forms. The author disapproves of a schematic, routine performance of prophylactic block dissection of the neck glands which, however, is indicated in some cases, among other reasons because of the difficulties of the clinical diagnosis. The necessity of individualizing the treatment is emphasized, taking consideration of the curability of the primary tumor, the presence of other metastases, the radical operability of the gland metastases, the age, general condition and possibilities for careful observation of the patient.

ZUSAMMENFASSUNG

Nach einer kurzen Beschreibung der Topographie der Lymphknoten des Halses wird über die Schwierigkeiten der klinischen Diagnose und die häufige Unstimmigkeit der klinischen und histologischen Befunde berichtet. In dem vorliegenden Material von 118 Patienten (Lippen- und Mundhöhlenkrebs sowie eine Anzahl anderer Tumoren) bestätigte die histologische Untersuchung die klinische Diagnose in 79.7 %, während in 20.3 % keine Metastasen vorlagen. Die Mehrzahl der Kranken war vorher radiologisch behandelt worden; in 17.2 % fand man sehr ausgesprochene Strahlenwirkung.

Darauf wird über die verwendete chirurgische Behandlung berichtet. Totale Entfernung der Halsdrüsen in einem Stück (ad modum Roux-Berger) wurde an 104 Kranken vorgenommen, darunter bei 9 Kranken beiderseitig, im ganzen also 113 in-einem-Stück-Resektionen mit einer Operationsmortalität von 1.8 %. Verf. glaubt, dass die Operationsmortalität bei mehr konservativer Indikationsstellung praktisch beseitigt werden kann. Von den 104 Kranken sind 41.3 % z. Z. symptomfrei, während 48.1 % an Krebs gestorben sind (Beobachtungszeit 1—12 Jahre).

Die Ergebnisse nach 3- bzw. 5-jähriger Beobachtung sind: bei Lippenkrebs 82.6 % und 80 %, bei Mundhöhlenkrebs 38.5 % und 33.3 %, bei anderen Tumoren 35.7 % und 37.5 % und im Gesamtmaterial 51.3 % und 50 % Symptomfreie. Im ganzen sind 50 Kranke an oder mit ihren malignen Tumoren gestorben. In 19 Fällen war der Tod durch Fortschreiten des Primärtumors bedingt, in 16 Fällen durch Rezidive oder Fortschreiten von Drüsenmetastasen und in 15 Fällen durch weiter entfernte Metastasen. Symptomfrei in der operierten lokalen Drüsenregion nach 3 Jahren: bei Lippenkrebs 87 %, bei Mundhöhlenkrebs 87.2 %, bei anderen Tumoren 78.6 % und im Gesamtmaterial 85.5 %. Es wird die Bedeutung einer vorhergehenden oder nachfolgenden radiologischen Behandlung betont.

Schliesslich werden die Indikationen der in-einem-Stück-Ausschälung bei den verschiedenen Tumorformen besprochen. Verf. nimmt Abstand von einer schematischen, routinemässigen Ausführung einer prophylaktischen in-einem-Stück-Ausschälung der Halsdrüsen, die jedoch in gewissen Fällen indiziert ist, u. a. wegen der Schwierigkeit der klinischen Diagnose. Die Notwendigkeit individualisierender Behandlung wird betont, bei der die Heilbarkeit des Primärtumors, die Gegenwart anderweitiger Metastasen, die radikale Operabilität der Drüsenmetastasen, Alter, Kräftezustand und die Möglichkeit einer sorgfältigen Beobachtung des Kranken in Erwägung gezogen werden.

RÉSUMÉ

Après une courte description de la topographie des ganglions lymphatiques cervicaux, l'auteur mentionne les difficultés du diagnostic clinique et les discordances fréquentes

existant entre celui-ci et les résultats de l'examen histologique. Dans le matériel de 118 cas dont il s'agit ici (carcinomes des lèvres, de la cavité buccale et un certain nombre d'autres tumeurs) l'examen histologique a confirmé le diagnostic clinique dans 79.7 % des cas, tandis que dans 20.3 %, il ne s'agissait pas de métastases. La plupart des malades avaient subi un traitement préalable aux rayons. Dans 17.2 % des cas, on a constaté un effet très accusé de l'irradiation.

L'auteur résume ensuite le traitement chirurgical employé. La dissection totale du bloc des ganglions cervicaux (méthode ROUX-BERGER) a été exécutée dans 104 cas, chez neuf d'entre eux dissection bilatérale, donc en tout 113 dissections totales du bloc ganglionnaire avec une mortalité postopératoire de 1.8 %. L'auteur croit qu'avec une thérapeutique à indications plus conservatrices, la mortalité pourrait être complètement éliminée. Des 104 malades 41.3 % sont actuellement sans symptômes. 18.1 % sont morts de cancer (période d'observation: de 1 à 12 ans).

Les résultats notés au bout d'un temps d'observation de 3 et 5 ans sont respectivement: dans le carcinome des lèvres 82.6 % et 80 %, dans le carcinome de la cavité buccale 38.5 % et 33.3 %, dans les autres tumeurs 35.7 % et 37.5 % et pour le matériel total 51.3 % et 50 % sans symptômes. 50 malades en tout sont morts porteurs de carcinomes ou à cause de lui. Dans 19 cas la mort a été due à la progression de la tumeur primitive, dans 16 cas à des récidives ou à la progression de métastases ganglionnaires, dans 15 cas à des métastases distantes. Absence de symptômes dans la région des ganglions locaux opérés au bout de 3 ans: dans le carcinome des lèvres, 87 %, dans le carcinome de la cavité buccale, 87.2 % autres tumeurs, 78.6 % et dans tout le matériel, 85.5 %. L'auteur souligne l'importance du traitement radiologique antérieur ou postérieur à l'opération.

Enfin il examine les indications de la dissection totale du bloc ganglionnaire cervical dans les diverses formes de tumeurs. L'auteur critique la pratique routinière et schématique de la dissection totale des ganglions cervicaux qui est cependant indiquée dans quelques cas, entre autres à cause des difficultés du diagnostique clinique. Il souligne la nécessité d'individualiser le traitement, en tenant compte de la curabilité de la tumeur primaire, de la présence d'autres métastases, de la pratique de l'opération radicale des métastases ganglionnaires, de l'âge, de l'état général et des possibilités d'observation suivie et attentive du malade.

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FROM THE MARIESTAD HOSPITAL, MARIESTAD, SWEDEN (PHYSICIAN-IN-CHIEF: G. BAUER, M. D.)

OBSERVATIONS ON THE TECHNIQUE OF PHLEBOGRAPHY[1]

by

Gunnar Bauer

With the discovery in recent years of the specific antithrombotic agents heparin and dicoumarol it has become a matter of great importance that incipient thrombotic processes in the lower limbs should be diagnosed as early as possible, since the substances in question will then have the greatest chance to be of service. For this purpose the roentgenologic method has proved to be decidedly more effective than all other clinical procedures hitherto in use; with phlebography, a sure diagnosis can as a rule be made long before the clinical methods can furnish reliable information.

It is very probable, therefore, that as our knowledge of the thromboembolic disease increases phlebography will in the future become a method of wide application. The reason why the method has not yet come into more general use in Sweden, except in one or two hospitals, lies partly in the present difficulty in procuring a suitable contrast medium, and partly also in the fact that in all probability there has existed among roentgenologists some degree of uncertainty with regard both to the best technique to adopt and the interpreting of the phlebograms obtained.

At the Mariestad Hospital, where phlebography was first employed in 1938, and where up to the present about 500 of these examinations have been carried out, a fairly wide experience has accumulated, and the aim of this paper is to examine to what extent this experience can throw light on the questions outlined above.

Contrast medium

Of all the drugs tried hitherto Perabrodil (or Diodrast) seems to be the best for phlebography of the legs. The reason for this is that

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neither the 35 per cent solution commonly employed nor the 50 per cent solution produces the slightest pain or venous spasm. By far the greatest number of phlebographies at the Mariestad Hospital have been made with this contrast medium. Perabrodil is not irreplaceable, however. When the supplies of it began to run low in 1944 we began experimenting with other contrast substances, and found that Intron[1] was a fully usable substitute, if it was diluted with equal parts of physiologic saline. This mixture has been used on about thirty patients. The films are the same as those obtained when perabrodil is used and the density of the contrast shadow is on the whole quite as good. The medium is well tolerated by the patients. Most of them feel not the least pain. In a few instances, on the other hand, there arose at the conclusion of the injection (and after both films had been taken) a more or less intense cramp-like pain in the calf which disappeared immediately, however, if 10—20 cc. of physiologic saline was injected through the needle still lying in the vein. Phlebography with diluted intron is therefore being used at present at our hospital as the standard method in all routine cases.

Technique

From the beginning, the technique used at Mariestad Hospital for phlebography has been to inject the contrast medium through an exposed vein behind the lateral malleolus and to take roentgenograms with the whole leg in the horizontal position. In the early days, sagittal projection only was used for the exposures. It was soon found, however, that the phlebograms obtained were difficult to interpret in some cases. We therefore changed over to stereography, which was tried for one year. Many doubtful cases were cleared up with this method, but the result was nevertheless not ideal. The ideal solution of the problem was only found when, at the end of 1941, we began to use two exposures, one with sagittal and the other with frontal projection.

The technical details of this method have been described in an earlier publication (1).

Phlebography can also be made by another method, however. In a paper published in 1941, LINDBLOM (2) described investigations carried out with the lower leg in the vertical position, injection of the contrast fluid after percutaneous venipuncture on the big toe, and horizontal projection of the ray. Beautiful films were obtained with this technique also. Since that date, HELLSTEN (3) has also used this method for some of his cases.

[1] A Swedish preparation (Tika), consisting of the sodium salt of diiodomethane sulfonic acid.

When deciding which of these two methods should be employed in phlebography various considerations must be kept in mind. It seems to me, that with patients suspected of having thrombosis and often confined to bed, such as are in question here, patients who often have a cyanotically discoloured, swollen, or aching leg, there is a certain amount of risk in placing them in a sitting position or allowing them to lie with the lower leg hanging down over the edge of the table, as must be done to obtain a perfectly vertical position of the lower leg. Not infrequently also, these patients have a fracture of the leg. It would seem to be a distinct advantage to be able to make the examination without having to move the patient from his recumbent position.

Further, with regard to the actual technique of injection I have, paradoxically enough, gained the impression that this is easier when the vein is exposed than when it is punctured. No difficulty whatsoever need be experienced in making the necessary infinitesimal incision in the skin behind the lateral malleolus and then freeing the selected vein. With this technique, there is the advantage of having at one's disposal a vessel of fairly large calibre which can be readily punctured in full view. The point of the needle can be fixed in the vein with a loosely tied ligature and the injection made without hurry or any particular risk that the cannula will slip out or the injection fluid infiltrate surrounding tissues. Among almost 500 patients only one has presented a small area of necrosis in the tissue due to extravascular infiltration. The intervention is so simple that it can be performed by any medical man who has seen it done once. To inject into a big toe vein can hardly be said to be a simpler procedure. A considerable amount of practice is undoubtedly necessary to be able to puncture this vein and then hold the point of the needle immovably fixed in it during the whole time the injection is in progress. There must be a risk that contrast medium will be deposited outside the vein also. In LINDBLOM's paper there is no mention of whether soft tissue necrosis occurred or not, but HELLSTEN reports that he has observed it. Furthermore, it is often necessary for the patient to hold his foot for a long time in warm water for the purpose of obtaining adequate swelling of the vein to be used for puncture.

In point of principle, it is, in my opinion at least, more attractive to inject the contrast fluid directly into an exposed vessel which one has under one's eye. In this way, the margin of error will be less, just as it is less if, in arteriography of a limb, for instance, one exposes the main artery instead of attempting to puncture it percutaneously.

All things considered, therefore, it would seem as if the method with the leg in a horizontal position and exposure of the vein were distinctly to be preferred from both the clinical and the practical standpoint.

The advantages and disadvantages of the respective phlebographic methods, described above, would, however, be of little significance if it could be proved that there are essential differences in the value of the roentgenograms obtained. An examination of the latter aspect seems justified, therefore, in the present discussion.

Interpretation of the phlebogram

It can now be safely stated that no doubt whatever exists about the fact that complete absence of the shadows of the deep venous trunks means that these trunks are occluded by thrombotic masses. (Fig. 2.) If, on the other hand, the shadows are visualized intact along their entire length thrombosis cannot be present. (Fig. 1.)

The large majority of phlebograms are of this type; there is no difficulty in interpreting them, and they can be obtained equally well with either of the two techniques of injection. To me, however, it would seem that the films with the leg horizontal are simpler and more easily evaluated. As the contrast medium, with this technique, is injected into a vein leading direct into the deep stems, we obtain a picture which, when there is no thrombosis, shows these trunks and almost nothing else, as may be seen from the typical phlebogram reproduced in figure 1. In the case of the film taken with the lower leg vertically placed, on the other hand, we obtain opacification also of veins of secondary importance (such as those accompanying the sural and tibial arteries, and pure muscle veins) and of superficial veins which, because of the venous stasis, can become so distended that they to a certain extent cover and complicate the picture of the deep venous system. Confusion between superficial and deep trunks is not impossible. It is, however, the trunks of the deep system, and them alone, which we want to examine, and the phlebograms obtained from the vertically placed leg therefore counteract this purpose through their very intricacy of detail. In any case, however, here it may be merely a matter of trifling points which the experienced observer will have no difficulty in interpreting.

Besides the above-mentioned, clearly positive or negative phlebograms there are always a not inconsiderable number of roentgenograms in which the shadows of the deep veins in the lower leg show *defects* of one kind or another. The interpretation of these can be more difficult. The chief reason for the occurrence of these defects must, of course, be that in certain segments of the deep venous system the blood containing the contrast fluid has been displaced by thrombotic masses in the vascular lumen. In actual fact, it is not surprising that such pictures should be encountered comparatively often, seeing that the object of the examination is to detect the thrombosis in its incipient phase. As,

1 a. 1 b. 2 a. 2 b.

Fig. 1. Normal phlebogram of leg and lower part of thigh. Leg in horizontal position. a) Sagittal projection. b) Frontal projection.

Fig. 2. No visualization of deep vein stems of lower leg. a) Sagittal projection. b) Frontal projection.

3 a. 3 b. 4 a. 4 b.

Fig. 3. Small defect in contrast shadow due to sedimentation, arising either at the entry of a tributary or on account of a small bend in the vein stem. a) Sagittal projection. b) Frontal projection.

Fig. 4. Bubble-shaped breaks in the contrast shadow due to thrombosis. a) Sagittal projection. b) Frontal projection. — Clinically established thrombosis.

according to the present consensus of opinion, the beginning stage consists of a small clot in a muscle vein which grows out into the main trunk and in this vein, as the result of gradual deposition, increases both in calibre, and in length, in the direction of the blood stream, it is obvious that the early stage of thrombosis will be reflected in the roentgenogram first as a thinning or a defect in the vein shadow and later on as a disappearance of entire sections of this shadow. As a matter of fact, when all the deep veins are blocked, we are already confronted with a fairly advanced stage of the thrombotic disease.

The interpretation would therefore be very simple if it were not for the existence of another reason for the formation of defects. LINDBLOM (2) has pointed out that certain peculiar defects or rarefactions can be present in the vein shadows even when there is no thrombosis, if the leg is in the horizontal position and the ray directed vertically (sagittally) when the films are exposed. He has also shown that the explanation of these irregulations lies in sedimentation phenomena arising through the fact that the specific gravity of perabrodil is higher than that of blood. Later, KJELLBERG (4), in an interesting experimental investigation, demonstrated the exact mechanism occurring in the production of these pictures.

Fig. 5. No visualization of deep venous trunks in middle third of lower leg, due to thrombosis. — Within 2 days, phlegmasia alba dolens.

One type of apparent absence of contrast medium in a vein is due to the fact that in some segments of the vein the fluid, without becoming mixed with the blood, flows along the bottom (the back) of the vessel in the form of a fine channel. These protions of the vein are therefore visualized on the phlebogram as a fairly fine line. As a broad vein shadow can sometimes pass over into a thin line of this kind, and then perhaps ten or twenty centimetres higher up revert to its original thickness it seems natural, for those unacquainted with this fact, to interpret the picture as an indication of thrombotic obstruc-

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6 a. 6 b. 7 a. 7 b.

Fig. 6. A break 4 cm. in length in the shadow of a vein stem, due to thrombosis. This defect is clearly visible in the profile view also. a) Sagittal projection. b) Frontal projection. — Clinically established thrombosis.

Fig. 7. a) Wide-spread, bubble-shaped defects in entire deep venous system of lower leg. That these irregularities were due to thrombosis was proved by a control venographic examination. b) Same leg, 4 days later. Complete absence of all deep vein shadows. — Clinically established thrombosis. This finding was verified at autopsy 3 years later.

tion of the lumen. In the early days of our investigations, I misinterpreted a few cases in this way. After a further close study of the phlebograms, it has been realized that they showed perfectly normal conditions. Profile views, taken with horizontal projection, are also of assistance for understanding the pictures. It must be borne in mind, however, that in phlebograms obtained from a leg in the horizontal position the veins are to be regarded as normal even when they are represented only by a thin line no thicker than the lead in a lead pencil. This feature is generally seen in the upper part of the lower leg, in the part of the vein lying between the junction of the two trunks of the fibular vein and up to and a little beyond the level of the knee-joint space. (Fig. 1.) Thus, no diagnostic difficulties need arise as a result of this phenomenon so long as one knows of its existence.

The other type of apparent defects in the contrast shadow consists of small rarefied areas in an otherwise well-visualized venous system, which sometimes occur in normal subjects if the leg is placed in the horizontal position and roentgenographed by vertical projection only. KJELLBERG has shown that these rarefactions occur at points where blood containing no contrast flows into the main trunk from a large side branch. These »defects» (Fig. 3)[1] are always of moderate dimensions, however, in most instances never more than a couple of centimetres in length, and are not visualized in profile views. Because of this, they are usually easy to distinguish from genuine defects due to the presence of thrombotic masses (Figs. 4, 5, 6, 7) and are therefore hardly likely to give rise to difficulties in the interpretation of the phlebograms.

Figures 4, 5, 6, and 7 plainly show that it is going a little too far to claim, as LINDBLOM (2, 5) does, that phlebograms obtained from horizontally placed legs can yield a sure, positive diagnosis of thrombosis only if »they show a total absence of contrast in the deep veins».

I shall now discuss other features of my material which might be brought forward to meet this statement of LINDBLOM's.

At the Mariestad Hospital, 180 patients were phlebographed during the years 1939—1944 on the clinical suspicion of incipient thrombosis of the lower leg.

In 73 of these patients the deep venous trunks were not visualized at all and the presence of thrombosis was therefore considered to be established.

In 62 patients the veins were so well filled with contrast fluid that they were regarded as normal and free from thrombosis. Only in 44

[1] The figure shows the largest defect of this type observed in my material. Not even here, however, is it possible to decide with certainty whether any sedimentation effect was in question. The picture may also be due to a slight bend in the vein, seen in the profile view. .

of these 62 patients, however, was the opacification absolutely perfect. In the remaining 18 there was slight irregularity in the contrast shadow in the form of segments with only a thin line of contrast (10 cases), or small local rarefactions in the shadow (6 cases), or a combination of both these features (2 cases). Not even in these 18 cases, however, was there any great difficulty in making the diagnosis. The profile view, taken with frontal projection of the ray, was of assistance, but only in three cases was it absolutely necessary. That the diagnosis of freedom from thrombosis was correct in these cases seems proved by the fact that although none of the patients received anti-thrombotic treatment none of them subsequently displayed clinical signs of thrombosis.

In 45 patients the defects in the contrast shadow were such that they were diagnosed as being due to the presence of thrombi. In 18 instances there was complete absence of a long segment of one of the main stems. Not even the finest line of shadow was to be seen in this area. In many cases the portion of the vein below this area (seen both on the films taken with sagittal projection and those with frontal projection) was considerably distended, indicating the presence of an obstacle immediately above, whereas the part of the vein above the break was of normal width and seemed to be receiving the contrast fluid from an incoming branch. (Fig. 5.) Pictures of this kind seem to me to point clearly to the presence of an occluding thrombosis. In the other 27 patients the irregularities in the shadow were of an entirely different kind. They consisted of long, bubble-shaped rarefactions in the vein shadow with in some places sharply outlined, in others seemingly obliterated, borders. In many cases these abnormalities were to be seen along the entire length of a venous trunk, or above or below a vein segment which was not opacified. In all cases where profile views were taken the same features were apparent. (Figs. 4, 6.) There seems no other reasonable explanation of these breaks in the contrast shadow than that they were due to thrombotic masses which were not wholly occluding the lumen and which partly adhered to the vessel wall, partly floated free in the blood stream.

In the attempt to prove that the breaks in the contrast shadow described above are not a sedimentation phenomenon but are really caused by incipient thrombosis many facts may be mentioned. Thus, 11 of the 12 patients who were submitted to phlebography before heparin treatment was instituted developed a typical phlegmasia alba dolens within 1—3 days, and the finding from the leg must therefore have constituted the initial stage of the total thrombosis of the leg. Since the introduction of heparin therapy we have had no cases in which the process has spread to the thigh, but other examinations have instead confirmed the diagnosis. In the early days, we were anxious to obtain verification by making another phlebography, and this was carried out in

10 instances, 1—10 days after the first. In all cases the control phlebograms showed larger gaps in the contrast line or complete absence of all the deep venous stems in the lower leg. (Fig. 7.) A second phlebography, therefore, is now considered unnecessary. In 6 patients the occurrence of pulmonary embolism was regarded as confirmation of the diagnosis. In 15 patients the diagnosis, while not proved, was extremely probable. These were patients from whom profile views were obtained showing the same roentgenologic abnormalities as those in the films for which sagittal projection was used, and in whom the clinical signs and symptoms were directly indicative of thrombosis. On going through the material, I can only find three cases from the early days of our phlebographic studies where it was not possible definitely to establish the presence of thrombosis; profile views had not been taken and the clinical signs and symptoms were not absolutely unequivocal.

Summing up, therefore, it can be said that of 45 patients showing incompletely visualized vein shadows of the above-mentioned type, there were 42 who had either definitely established or very probable incipient thrombosis. From this it will be seen that phlebography with the leg in the horizontal position is by no means liable to lead to wrong conclusions. So long as we are acquainted with the appearance of the so-called sedimentation pictures and avoid this source of error the method can be used with perfect safety for diagnosing thrombosis both in its incipient and in its more advanced stage.

In conclusion, it can be mentioned that HELLSTEN (3), in his exhaustive phlebographic studies from the year 1942, also came to the conclusion that films taken with the leg horizontal are »fully adequate for the purpose of interpretation».

SUMMARY

On the basis of the findings from a series of almost 500 personally conducted phlebographic examinations, 180 of which were on patients suspected of having incipient thrombosis of the leg, the author discusses a number of questions of interest in this field. Perabrodil or Diodrast is believed to be the best contrast medium. Intron, diluted with equal parts of physiologic saline, can also be used, provided that facilities are at hand for flushing the venous system with saline if the patient experiences pain. With regard to the technique of phlebography, it is recommended that a retromalleolar vein be exposed and the contrast fluid injected into this; this technique is easier and in all probability involves less risk than percutaneous puncture of a vein on the big toe. The author furthermore prefers to make the roentgenographic examination with the patient's leg in the horizontal position. To place the lower leg in the vertical position is considered disadvantageous from the clinical standpoint. Films taken with sagittal projection should always be complemented with a film taken with frontal projection. When the phlebography is carried out with the leg in the horizontal position there are sometimes seen in the phlebograms certain characteristic rarefactions, or diminution in density, in the vein shadows, caused by the tendency of the contrast fluid to form sediment. They are easily recognizable, however, and no difficulties need arise in differentiating

them from the typical defects in the contrast shadow due to the presence of fresh clots in the veins.

ZUSAMMENFASSUNG

An Hand der Befunde bei einer Reihe von fast 500 persönlich geleiteten phlebographischen Untersuchungen, von denen 180 an Kranken vorgenommen wurden, bei denen Verdacht auf beginnende Thrombose des Beines vorlag, bespricht Verf. eine Anzahl interessanter Fragen auf diesem Gebiete. Per-Abrodil oder Diodrast hält er für das beste Kontrastmittel. Auch Intron, zu gleichen Teilen mit physiologischer Kochsalzlösung verdünnt, kann Verwendung finden, vorausgesetzt dass Anordnungen bei der Hand sind, um, falls der Patient Schmerzen verspürt, das Venensystem mit Kochsalzlösung zu überschwemmen. Was die Technik der Phlebographie betrifft, wird empfohlen, eine retromalleolare Vene freizulegen und das Kontrastmittel in diese einzuspritzen. Diese Technik ist leichter und bringt allem Anschein nach weniger Gefahren mit sich als die perkutane Punktion einer Vene an der grossen Zehe. Ferner zieht Verf. es vor, die röntgenographische Untersuchung bei wagerechter Lage des Beines des Patienten vorzunehmen. Den Unterschenkel in senkrechte Lage zu bringen, wird in klinischer Hinsicht als unvorteilhaft bezeichnet. In sagittaler Projektion aufgenommene Bilder sollten immer mit einem in frontaler Projektion aufgenommenen vervollständigt werden. Wenn die Phlebographie am horizontal gestellten Bein vorgenommen wird, sieht man in den Phlebogrammen manchmal gewisse charakteristische Aufhellungen oder weniger dichte Stellen in den Venenschatten, die durch die Neigung der Kontrastflüssigkeit zur Sedimentierung bedingt sind. Sie sind jedoch leicht erkennbar und lassen sich unschwer von den durch die Gegenwart frischer Gerinnsel in den Venen verursachten typischen Defekten im Kontrastschatten unterscheiden.

RÉSUMÉ

Sur la base des résultats d'une série d'au moins 500 examens phlébographiques personnels, dont 180 sur des malades chez lesquels on soupçonnait un début de thrombose des jambes, l'auteur discute un certain nombre de questions intéressant ce domaine. Il estime que les meilleurs opacifiants sont le perabrodil ou le diodraste. On peut aussi se servir de l'intron dilué dans parties égales de solution physiologique mais en ayant soin d'avoir à portée une quantité suffisante de solution physiologique pour irriguer le système veineux au cas où le malade accuse des douleurs. En ce qui concerne la technique de la phlébographie, l'auteur conseille de découvrir un veine rétro-malléolaire et d'y injecter l'opacifiant; ce procédé est plus facile et comporte probablement moins de risques que la piqure transcutanée d'une veine du gros orteil. En outre l'auteur préfère pratiquer l'examen radiologique sur la jambe du malade en position horizontale. Placer la jambe à partir du genou en position verticale a des inconvénients du point de vue clinique. Des films pris de profil devraient toujours être complétés par des prises de vue frontales. Quand on pratique la phlébographie avec la jambe en position horizontale, on observe parfois dans le phlébogramme certaines zônes caractéristiques de raréfaction ou de diminution de densité dans les ombres veineuses qui sont causées par la tendance de l'opacifiant à former des sédiments. Cependant il est facile de les distinguer des ombres dues à la présence de caillots frais dans les veines.

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FROM THE NORWEGIAN RADIUM HOSPITAL, OSLO (CHIEF: ROLF BULL ENGELSTAD, M. D.)

THE TREATMENT OF TUMORS OF THE URINARY BLADDER[1]

by

Rolf Weyde

The treatment of tumors of the urinary bladder is a discouraging task presenting numerous problems, and so far moderate results have been obtained. Combined surgical-radiological treatment has however, in recent years considerably improved the results, and the possibilities of further advancement by this method are present.

The material we are able to present from the 11 first years after The Norwegian Radium Hospital was opened is distinctly poor and very heterogeneous. However, when we have found reasons for commenting on it at all, it is on account of experiences gained which may have a claim on our interest.

In the years 1932 to 1942 a total of 157 patients with tumors of the bladder have been treated. 2 patients have continued their treatment at other hospitals and information of their further fate is lacking. The total number we are thus able to present is 155, 97 men and 58 women. The age incidence of the patients was on admission to the hospital on the average quite high, as 98 patients were above 60 years of age. Regarding the men the average age being 57.5, the women 60.4. The distribution as to their age is evident from the following table.

Table I.

Men:		Women:	
6 years	1		
20—29 »	2		
30—39 »	5	30—39 years	4
40—49 »	16	40—49 »	6
50—59 »	19	50—59 »	14
60—69 »	35	60—69 »	26
70—79 »	15	70—79 »	6
80—89 »	4	80—89 »	2

[1] In an abbreviated form read as a lecture at the meeting of Oslo Surgical Association 19. 2. 45, submitted for publication, March 15, 1945.

Advanced age and poor general condition have in many cases been a counter-indication against surgical intervention. On admission, a great majority of the patients had a far advanced carcinoma of the bladder which frequently had been treated several times before-hand, and consequently were no longer suitable for radical surgery. 53 of these cases were in such poor condition that even an attempt at palliative roentgen therapy was either considered useless, or had to be discontinued after quite inadequate doses, owing to anemia, fever or uremia.

The diagnosis is based on the cystoscopical appearance of the tumor and the findings after cystotomy, the age of the patient at the onset of the disease, and the progress of the disease. In 68 patients ulcero-infiltrating types of bladder carcinomas were manifest, whereas 69 are registered as malignant papillomatas or papillomatous carcinomas. However, our attention is here drawn to the fact that several of the last mentioned types had somewhat extensive infiltrations to the wall of the bladder, whereas others are included in this group because their anamnesis showed a verified papilloma in the past. The histological examination has given proof of the correctness of the diagnosis in the cases where infiltrating growth of the epithelium had been ascertained. It will however, be well known that the histological examination regarding this disease is very complicated and often proves a failure. This is first due to purely technical difficulties connected with the procuration of a serviceable biopsy specimen through the cystoscope, but secondly certain conditions exist regarding these tumors, especially concerning the histology of the papillomatous tumors, that complicates the determination as to the malignancy of the growth. Thus it is not unusual that the histologist is unable to prove infiltrating growth of the epithelium, even though he has been provided with the entire tumor and its pedicle, and yet the tumor in its further progress exhibits the clinical picture of a very malignant growth. Consequently, when the treatment is planned one must first of all consider the clinical findings, the appearance and propagation of the tumor, as well as the age of the patient.

Before proceeding into a closer discussion of our material I will briefly mention the principles in our treatment of tumors of the bladder. These have changed somewhat in the course of the years. In the first 5 to 6 years after the hospital was opened, the patients received primary roentgen therapy more commonly than to-day. With our present indicative position we would undoubtedly now have given several of these patients combined surgical-radiological treatment. In the same period of time, the roentgen doses, compared to our present experiences, were as a rule too small. Of the 38 patients mentioned in table III as having received a too low tumor dose, 30 had been treated before 1937. The irradiation technique has otherwise practically been the same all

the time. We administer protracted-fractional irradiation on 4 fields against the bladder, 2 frontal fields and 2 back fields. Perineal field has generally not been used. The treatment is given daily on one field with single dose up to 350 r in skin dose, having in cases with severe cystitic troubles, had to proceed more carefully in attaining if possible a total dose of at least 3,500 r on each field. The tumor-dose has in recent years been measured, and a dose of approximately 150 r has been given daily. If the tumor-dose got too large, the daily irradiation was divided on 2 fields. As a total tumor-dose we try to attain approximately 5,500 r or more. The irradiation factors are 175 kV, 4 ma, 50 cm FS-distance, 1 mm Cu filter. These factors of irradiations and the dosageing are principally the same if the treatment is given as sole treatment, pre-operative or post-operative irradiation, respectively.

During the first couple of years different methods of radium treatment were attempted in a few cases, but soon abandoned. This included e. g. radium inserted in a Nelaton's catheter by the urethra or radium application after cystotomy, either on a mould against the wall of the bladder or enclosed in a rubber drain. In a few cases teleradium treatment against the bladder was also attempted, on 2 fields over the symphysis.

Electro-coagulation through the cystoscope was for several years more extensively in use than at present in the treatment of larger tumors. The indications for this intervention have by and by been considerably reduced to the advantage of »open» electro-coagulation subsequent to cystotomy. We now electro-coagulate through the cystoscope only very small papillomatous tumors with narrow, not infiltrated pedicle and base. This will in practice most often concern early recurrences discovered at the routine control examination of our patients. Exceptionally somewhat larger tumors are being treated by this method, if for some reason cystotomy is counter-indicated.

In short, the following might be said about the lines of direction we follow at present in the treatment of bladder tumors: (Cit. BULL ENGELSTAD).[1]

In young people with one or a few quite small papillomatas one might be justified in attempting electro-coagulation through the cystoscope on condition that the patient is kept under close observation. In young ones with larger and more widespread papillomatas, one may perform a cystotomy and make a radical electro-coagulation, if necessary with a subsequent intubation of radium needles into the wound-bed. In certain cases one may be justified in giving roentgen treatment exclusively.

[1] BULL ENGELSTAD, ROLF: Lærebok i stråletherapi (Manuskript).

Regarding middle aged and older people, papillomatas of the bladder are always treated as a carcinoma. The same is the case in young individuals with larger and more widespread papillomatas, on account of the danger of recurrences and the possibility of subsequent malignant development. If the tumor is localized to the »free» part of the bladder, resection may be done, followed by post-operative roentgen irradiation. However, as most bladder tumors are localized in the floor of the bladder and its adjacent parts, one has generally only the choice of a radical removal of the bladder, elctrocoagulation combined with radiotherapy or radio-therapy alone. Radical removal of the bladder is, however, a most mutilating intervention where, even after operations performed by the most skilled hands, the operative mortality is discourageingly high. The results obtained from radio-therapy alone are very moderate. Accordingly, if the general condition of the patient permits it, and the cystoscopical findings reveal that there are possibilities of carrying through a radical electro-coagulation of the tumor, our method at present, similar to that of several other clinics, is cystotomy, electrocoagulation of tumor, intubation of radium needles in the wound-bed, and post-operative roentgen therapy as soon as the incision is healed. We intubate radium needles à 10 mg. Radium Element evenly distributed under the wound-bed, $^3/_4$ to 1 cm. apart. The needles are attached to metal wires which are brought out through the incision, this is then completely closed except for a small tampon to Retzius' space. With the filtering we use in our radium needles (1 mm. Pt) a sufficient tumor-dose is obtained by leaving the needles for 24 hours. The needles are then easily removed through the incisional wound by pulling them out by the wires. Any kind of anesthesia is not required. The patients keep permanent catheter until the incision is closed, get up and commence the post-operative roentgen treatment.

According to the circumstances one may be obliged to modify a few items in the consecutive order of the treatment. If the wall of the bladder is too thin one may for instance have to omit the intubation of radium needles. In one case where tumor after the cystotomy proved to be inoperable, we intubated radium needles without previous electrocoagulation of tumor. One may be obliged to postpone the post-operative roentgen treatment in case complications arise subsequent to the operation, or else we may have to discontinue and if necessary postpone the treatment in case the irradiation reaction in the bladder appears too soon, due to the additional radium reaction. The roentgen dose we have been able to give subsequent to the intubation of radium needles in the wall of the bladder has varied between 7,200 r divided on 4 fields (tumor-dose 2,500 r) and 14,850 r divided on 4 fields (tumor-dose 5,134 r).

As regards bladder tumors which are so widespread that we, according to the cystoscopical picture find we are unable to effectuate a radical electro-coagulation after cystotomy, we administer primary roentgen therapy. The results of this treatment will be accounted for below. We will only mention here that the tumors in some cases disappear completely, in other cases we observe that the tumors, 6 to 8 weeks after the termination of the roentgen treatment, have been so reduced that a radical electro-coagulation may be performed. In these cases as well we use radium intubation in the wound-bed if possible, and a renewed series of roentgen treatment if necessary. This combined method with radium-intubation in the wound-bed subsequent to electro-coagulation and followed by roentgen irradiation, has in the form we employ it at present, been worked out by the present chief of the hospital ROLF BULL ENGELSTAD M. D. in the years 1936—1937.

As previously mentioned, the treatment of tumors localized to the free part of the bladder, will in some cases be a resection. In the present material this intervention has only been performed 3 times. The question as to the possibility of a radical removal of the bladder, has been ventilated a few times, but the consulting surgeons have each time advised against it.

We will now first classify our material according to the primary treatment method, and a closer investigation of each one of these groups will indicate what has been achieved by this treatment. Table 2 gives a general view of the material.

Table II.

I.	Attempts at radium treatment during the first years at the hospital	8
II.	Untreated	24
III.	Roentgenologically treated	88
IV.	Surgically treated prior to admission. Post-operative roentgen therapy	17
V.	Surgically-radiologically treated at the Norwegian Radium Hospital	18

It may be discussed how one most adequately shall classify a material of this kind. We have chosen the present classification as it gives us the best general view of what is achieved by the different treatment methods. The 2 last groups, totaling 35 patients includes only papillomatous carcinomas, whereas group II and III comprises both ulcero-infiltrating types, and papillomatous carcinomas with more or less extensive infiltration or ulceration in the wall of the bladder. Regarding many of these far advanced carcinomas the classification was very problematical. We have therefore found it most correct to treat these patients in the same group.

Group I. The 8 patients included in this group will be discussed briefly. 5 had a far advanced intractable carcinoma of the bladder and got ra-

dium treatment mostly as an attempt, in the form of radium inserted through Nelaton's catheter by the urethra or in a rubber drain through the supra-pubic fistula. They all died within 6 months. In one patient with a malignant papilloma the size of a walnut, post-operative teleradium treatment was given subsequent to cystotomy and electro-coagulation. This patient lived symptom-free for 3 years when he died of apoplexy. In 2 cases, subsequent to cystotomy and electro-coagulation, application of radium on a mould made from Kerr's paste was tried against the wound-bed. The mould was removed 24 hours later through the cystotomy incision which had to be reopened. One of the patients died a few days after this intervention, the second was alive symptom-free 2½ years later, when we last were able to trace him. This method has not been reattempted. We now achieve radium irradiation of the wound-bed by a far simpler and less dangerous procedure, namely by intubation of radium needles, easily removeable without the necessity of reopening the incision.

Group II. This group comprises quite desolate cases, where any kind of treatment was considered of no value. All patients died within a short period of time, of from one week to 10 months, average duration of life being 3 months.

Group III. This largest group comprising 88 patients has been of special interest to us, as we here obtain facts of what the roentgen treatment may yield in tumors of the bladder. The results are classified in table III.

Table III.

88 roentgenologically treated.	A.	B.	C.	Total.
1. Primary symptom-free	0	6	8	14
a) Alive, still without recurrence		4	4	8
b) Recurrence, treated, alive without recurrence		0	1	1
c) Recurrence, dead		2	3	5
2. Tumor operable after roentgen therapy	0	4	7	11
3. Improved, living with carcinoma	0	2	3	5
4. Dead	29	14	15	58

Period of observation:

ad 1 a) 2 patients 7 years — 1 patient 3 years
2 » 6 » — 1 » 1½ »
1 » 4 » — 1 » 10 months.

In this table we have classified the patients both according to the results of the treatment and to the roentgen dose we have been able to administer in each case. Column A comprises patients where the treatment had to be discontinued after quite inadequate doses, due to anemia,

fever or uremia. One might have been quite justified in adding these patients to group II, the untreated ones. They gained little or no benefit from the treatment, and all died within a period of from 1 week to 22 months after the treatment was discontinued. Average duration of life was 4.4 months.

Column B includes those patients where the treatment was terminated with a tumor-dose considered too low, compared to our present demands whereas all the patients having received what we today consider a satisfactory dose, are classified in column C. The division between group B and C has perhaps been put down somewhat arbitrary with a tumor-dose of approximately 5,000 r. The numbers as will be noticed are practically equal in both groups, but being too small they do not permit us to draw any conclusions from it as regards the significance of the doses size. To this must be remarked that 30 of the 38 patients in group B were treated before 1937, a period in which we, as mentioned above, to a greater extent treated less advanced cases primarily with roentgen therapy. Most of these namely $14 + 15 = 29$ patients are in spite of having completed their treatment dead from their carcinoma of the bladder within a relatively short period of time of from 2 months to 4 years, average duration of life being approximately 10 months. However many of these have as a result of the treatment exhibited a shorter or longer lasting period of amelioration of some of the symptoms. The cystitis, and especially the hematuria, are often favourably affected, with, as a consequence, an increase in the percentage of hemoglobin and an improvement of the general condition. 5 patients mentioned as improved are still living with carcinoma of the bladder, after a period of observation of 5 years 5 months, 3 y. and 4 m., 1 y. and 3 m., 1 y., 9 m., respectively. The 2 first of these will briefly be referred as an illustrative example of the effects of the roentgen treatment.

1. Woman, 66 years of age. Cystoscopy revealed a widespread papillomatous tumor in the right side of the floor of the bladder and the right side wall. Biopsy (scanty specimen): Papilloma with atypia, carcinoma? Received roentgen treatment in several series, total skin dose 21,600 r divided on 4 fields in the course of approximately 3 years. Considerable reduction of tumor. In periods subjectively symptom-free and without hematuria. Living with her carcinoma, little inconvenienced after $5^1/_2$ years.

2. Man, 76 years of age. 4 months hematuria. Cystoscopy revealed an infiltrating slightly prominent tumor involving almost the entire trigonum and a part of the right side wall as far as the internal orifice of the urethra. Biopsy: Poorly differentiated carcinoma. Received roentgen treatment. Total dose 8,874 r divided on 2 frontal fields. (Small dose given owing to the advanced age of the patient.) He has refused to return for cystoscopic control examination on account of his high age. The patient is living subjectively symptom-free after 3 years and 4 months, with slight pyuria but no hematuria.

This last mentioned patient is registered as improved because we have no cystoscopic control examination after the termination of the

treatment. The effect of the treatment, is however, quite strikingly judged by the urinary findings and the subjective symptoms, especially considering the small dose administered.

There is of course no definite division between these patients and the following groups which are to be discussed, namely, those who have become primarily symptom-free and the ones where tumors have become operable subsequent to the roentgen treatment. As a matter of fact, we observe all transitional stages, from little or no improvement to considerable improvement and primary symptom-freeness, which in some cases may be permanent.

Of the 14 patients who became primary symptom-free, 5 later got recurrences and died from their carcinoma of the bladder after a duration of life of 6 months, 9 months, 1 year, 2 years, and 6 years, respectively. One patient got a recurrence in the form of a small papilloma localized in another part of the bladder, after cystoscopically being free from symptoms for $1^1/_2$ year. After electro-coagulation performed through the cystoscope the patient has now remained symptom-free for 1 year and 3 months after this last treatment.

8 patients are then remaining, being alive and free from recurrence with periods of observation as shown i table III. These cases will quite briefly be reported casuistically.

1. Woman, 56 years of age was admitted for inoperable carcinoma of the bladder wall. Cystoscopy revealed an ulcerative tumor with wide base the size of a walnut, localized in and behind the trigonum. Biopsy failed. Received roentgen treatment. Total dose 8,400 r divided on 4 fields. Complete disappearance of tumor. Free from recurrence $7^1/_2$ years.

2. Man, 55 years of age. Cystoscopy revealed the entire half of the bladder occupied by a nodular, slightly protruding tumor. The remaining part of the mucous membrane of the bladder was edematous and fibrin covered. Biopsy: Infiltrating growth of highly atypical epithelium growing in solid fibers. Diagnosis: carcinoma. Received roentgen treatment. 12,000 r divided on 4 fields. Tumor disappeared completely. Cystoscopically free from recurrence for 7 years.

3. Man, 49 years of age. Cystoscopy revealed almond-sized, broad based tumor localized in the orifice of the right ureter. Biopsy failed. Received roentgen treatment. 10,000 r divided on 4 fields. Complete disappearance of tumor. Cystoscopically free from recurrence 6 years.

4. Woman, 32 years of age. Repeatedly electro-coagulated for papillomatas of the bladder during several years. Cystoscopy revealed ulcerating tumor with nodular surface involving the entire trigonum. Biopsy (minimal specimen): Granulation tissue with abundance of cells. Diagnosis: Inflammation. Received roentgen treatment. 8,400 r divided on 4 fields. 4 months later bladder calculi was discovered and removed. Had lingering cystitical troubles. One year later, auto-vaccinated with fecal streptococcus bacilli. Gradual improvement. Alive, cystoscopically free from recurrence and subjectively symptom-free for 6 years.

5. Man, 73 years of age had hematuria during 4 years. Cystoscopy revealed large ulcerating tumor in left side of the floor of the bladder, and a palpable tumor above and

adherent to the prostate gland. No biopsy. Roentgen treatment given. 9,750 r divided on 4 fields. Symptom-free and cystoscopically free from recurrence for 4 years and 4 months.

6. Man, 65 years of age had had hematuria during 4 months. Prior to admission cystotomy and electro-coagulation of a papilloma. Biopsy: Papilloma with a moderate degree of atypia. Cystoscopy on admission revealed 2 protruding tumors approximately the size of a pea, directly in front of the orifice of the right ureter. These were interpreted as recurrences or remains of tumor. Roentgen treatment with a tumor dose of 5,146 r was given. 3 years cystoscopically free from recurrence.

7. Man, 68 years of age. Hematuria during 5 months. 4 months prior to admission cystotomy and electro-coagulation of a nut-sized tumor localized close to the orifice of the left ureter. Biopsy: Papilloma with atypia, indistinct division between epithelium and stroma, malignancy not improbable. Cystoscopy on admission revealed an extensive recurrence. Approximately one half of the floor of the bladder was occupied by a prominent tumor with an ulcerative surface. Roentgen treatment given with a tumor dose of 4,930 r. Cystoscopically free from recurrence $1^1/_2$ year.

8. Man, 78 years of age had had hematuria during 3 months, and 3 months prior to admission cystotomy and electro-coagulation of a papillomatous bladder tumor. Biopsy: Papillomatous carcinoma of the bladder, the stroma infiltrated by atypical epithelium containing some lymphocytes and plasma cells. Cystoscopy on admission revealed disc-like infiltration with an ulcerative center localized in the floor of the bladder, too advanced for a radical electro-coagulation. Roentgen treatment given. Tumor dose 5,080 r. Cystoscopically free from recurrence 10 months.

Case no. 2 is here of special interest as it concerns a 55-year-old man with a histologically verified infiltrating far advanced, and inoperable carcinoma of the bladder, which subsequent to roentgen therapy becomes free from symptoms, and is still free from recurrence after 7 years. HEUSCH[1] disputes having ever seen this kind of case cured by roentgen therapy, and mentions at the same time several others sharing his opinion. Our experience is, and we claim it is evident as well from the material presented here, that many carcinomas of the bladder exhibit such a decided radio-sensitivity that similar cases ought not to appear surprising, and will perhaps be seen more frequently with an improved technique. Cases nos. 7 and 8 as well, have shown a similarly favourable primary result of the treatment, but the period of observation is still too short, being only $1^1/_2$ years and 10 months, respectively. When strongly evidenced cases like these are rare, one of the reasons accounting for it, is the difficulty in procuring a sufficient biopsy specimen for histological examination. In the remaining 5 cases the histological proof of the correctness of the diagnosis is missing, and for this reason we will here let the morbid history speak for itself.

In table III was finally mentioned 11 patients where the tumor became operable subsequent to the roentgen treatment. The interventions made practicable were, in 2 cases electro-coagulation, 6 of whom got

[1] HEUSCH, KARL: Blasenkrebs, Leipzig 1942.

intubation of radium needles in the wound-bed. In one case operation became technically possible but could not be carried out owing to the advanced age and poor general condition of the patient. The results of this combined treatment method, roentgen therapy with subsequent surgical treatment are evident from the following table IV where observation periods and duration of life are put down in brackets.

Table IV.

Living, free from recurrence	2.	($3^1/_2$ years, 2 years)
Dead. Free from recurrence in the bladder	1.	(3 years).
Living with recurrence	2.	(2 years, 16 months).
Dead	5.	(3 years, 14 months, 8 months, 3 months and 3 months).

The one patient having been free from recurrence with observation period of $3^1/_2$ years will briefly be referred as an illustrating example of the effects of the treatment.

Man, 60 years of age with a tumor the size of a figue localized in the right side of the bladder at the orifice of the right ureter. Roentgen treatment given. Total dose 10,000 r divided on 4 fields. Considerable reduction of tumor to approximately nut-size. Cystotomy performed with electro-coagulation + intubation of radium needles à 10 mg. in 24 hours. Biopsy: Papilloma of the bladder with infiltrating growth, carcinoma probable. $2^1/_2$ years later operated on for bladder stones. Symptom-free $3^1/_2$ years.

Group IV. 17 patients were admitted for post-operative roentgen therapy subsequent to surgical treatment in other hospitals. Resection of the bladder had been performed in 3 cases, in the remaining 14 cases, cystotomy and electro-coagulation of tumor. Histological examination showed in 14 cases infiltrating carcinoma, in 2 cases malignant papillomatas (papilloma with infiltrating growth of atypical epithelium), and in 1 case papilloma with atypia. At the cystoscopical examination made prior to the commencement of the roentgen treatment, we could in 15 cases ascertain that the intervention apparently had been carried out radically, as we were unable to find any remains of tumor or any definite signs of recurrence but only cicatricial changes. Regarding 2 cases, Pezzer's catheter had been inserted in the bladder and cytoscopical examination thereby made impracticable. In this connection we shall want to emphasize, that in our opinion insertion of Pezzer's catheter in carcinoma of the bladder ought only be made in case of imperious necessity, for instance where the patients have persistent hemorrhage or urinary retention due to blood clots. A permanent cystotomy opening renders to a great extent the roentgen treatment difficult, and gives great discomfort to the patient on account of the shrinkage of the bladder. In these kind of cases we first will have to make an attempt at closing

the bladder fistula, and the roentgen treatment is not to be commenced until this is healed. If a closure for one reason or another seems impracticable one may as a rule omit the roentgen treatment, as it is then evident, that the local and general condition of the patient is so poor that one cannot count on being able to administer an effective roentgen dose. Regarding both our cases, the bladder fistula was closed and the treatment completed. In all the 17 cases the treatment was carried out according to routine method, as regards 10 patients however, with a tumor dose too low compared to our present demands. The treatment results are evident from table V, where the numbers in brackets show observation period and duration of life, respectively.

Table V.

Living free from recurrence	4.	(6 years, 2 years and 10 months, 2 years and 9 months, 1 year and 4 months).
Living free from recurrence after treatment for recurrence	2.	($4^1/_2$ years, 4 years).
Dead, free from recurrence in the bladder	4.	(4 years, $1^1/_2$ years, 7 months, 2 months).
Living with recurrence	1.	($2^1/_2$ years).
Dead from carcinoma of the bladder	6.	(6 years, 3 years, 1 year 8 months, 1 year 7 months, 9 months).

Of the 6 who are living free from recurrence 2 have later been retreated for recurrence with cystotomia and electro-coagulation, and are again living free from recurrence $4^1/_2$ and 4 years after the last treatment. The primary treatment was in 2 cases resection, and in 4 cases cystostomy with electro-coagulation. In all the cases histological examination revealed carcinoma. The roentgen treatment was completed without interruption, 2 patients however got a too low tumor-dose.

The 4 who are dead without recurrence in the bladder died from pneumonia, metastasis from carcinoma of the bladder, tuberculosis of the lungs, and ileus, respectively. For the last mentioned patient the observation period was only 2 months.

The one patient living with recurrence after $2^1/_2$ years was without evidence of recurrence 21 months after the roentgen treatment.

6 patients are dead from carcinoma of the bladder. Regarding 4 cases the recurrences appeared before 6 months, in one case after 9 months and in one case after 19 months.

These results must be regarded as satisfactory considering that the biopsy report in 16 cases revealed infiltrating growth of atypical epithelium, and in one case papilloma with atypia. How far the post-operative roentgen therapy may account for this result we dare not say. Our material has no basis of comparison permitting us to judge the benefits obtained by post-operative roentgen therapy in bladder tumors. How-

ever, when observing the sometimes considerable radio-sensitivity that particularly the papillomatous carcinomas, but also the infiltrating carcinomas of the bladder may have, it seems correct to give post-operative roentgen treatment as a routine method in all bladder tumors. Exceptions may of course be made in quite young individuals when special considerations make it advisable, as in papillomatas which are so small that electro-coagulation may be made through the cystoscope, on condition, however, that the patient is kept under close observation.

Group V. In table 2 we have classified as group V the 18 patients who all had papillomatous carcinomas and all of whom could be submitted to surgical or combined surgical-radiological treatment after admission to the Norwegian Radium Hospital. This group is unfortunately too small to give a numerically reliable expression of the results achieveable by this treatment method. This concerns especially the results obtained from the procedure which we today consider of the greatest interest to us, namely, electro-coagulation after cystotomy, radium intubation and postoperative roentgen treatment which was only attempted in 9 of the 18 patients. During operation one case proved to be inoperable, and radium intubation without electro-coagulation was attempted. In spite of subsequent roentgen treatment gradual progression set in, and the patient died after 4 months. In the remaining 8 cases electro-coagulation through the cystoscope was performed, and in 6 of these post-operative roentgen treatment was given. The treatment results concerning the 17 patients with tumors that could be radically electro-coagulated, are shown in table 6, observation period and duration of life, respectively are put down in brackets.

Table VI.

Living free from recurrence	7.	(10 years, 10 years, $9^1/_2$ years, 6 years, $4^1/_2$ years, $2^1/_2$ years and $2^1/_2$ years).
Living free from recurrence after treatment for recurrence	4.	(7 years, 6 years, 2 years, $^1/_2$ year).
Living with recurrence	3.	($2^1/_2$ years, $1^1/_2$ years, $1^1/_2$ years).
Dead	3.	(3 years, $1^1/_2$ years, $^1/_2$ year).

It is evident from this table that 11 of the patients are living free from recurrence with an observation period of from $^1/_2$ to 10 years. 6 are living free from recurrence being more than 5 years free from symptoms.

Of the 11 patients at present living free from symptoms, 7 were treated with electro-coagulation through the cystoscope, all received treatment in the first half of the period of time we have been revising here. The morbid history of these patients will briefly be referred.

1. Woman, 62 years of age was 4 years prior to admission electro-coagulated through the cystoscope for papilloma of the bladder. Biopsy: Carcinoma. On admission a recurrence the size of a pea. No biopsy. Free from recurrence 10 years.

2. Man, 49 years of age with broad-based tumor behind the orifice of the right ureter the size of a six-pence. Biopsy: infiltrating growth of very atypical tumor tissue. Carcinoma. Electro-coagulation and post-operative roentgen treatment. 6,500 r divided on 4 fields. 10 years free from recurrence.

3. Man, 55 years of age with large uneven ulceration behind the trigonum, as well as 2, approximately nut-sized groups of soft flagelating papillomatas. Biopsy: Papilloma with atypia. Carcinoma? Too sparse biopsy specimen for determination as to infiltrating growth. Electro-coagulation and roentgen treatment given. 8,600 r divided on 4 fields. Recurrence the size of a pea 2 years later. Again electro-coagulated through the cystoscope. Free from recurrence 6 years after the last electro-coagulation.

4. Man, 61 years of age with a conglomeration of papillomatas in an area the size of a walnut. Biopsy: Papilloma with atypia. (Minimal biopsy specimen.) Electro-coagulation and post-operative roentgen treatment given. 8,500 r divided on 4 fields. A quite small recurrence after 9 months. Again electro-coagulation and post-operative roentgen treatment. 8,000 r divided on 4 fields. Living free from recurrence 7 years.

5. Woman, 57 years of age with a $5^1/_2$ cm. large, comb-shaped papillomatous tumor on the hind wall of the bladder. Slight bleeding from tumor. Biopsy (Minimal specimen): Granulation tissue. Electro-coagulation and roentgen treatment given. 9,000 r on 4 fields. Free from recurrence 6 years.

6. Woman, 68 years of age, had 4 years prior to admission been electro-coagulated for a papilloma of the bladder. At present a papilloma the size of a walnut with broad base, localized close to the orifice of the left ureter. Biopsy: Papilloma with atypia (the bits of tissue being too small to determine infiltrating growth). Electro-coagulation and roentgen treatment. 8,000 r divided on 4 fields. During several years electro-coagulated for small recurrences at another hospital. At present living free from recurrence 2 years after the last treatment for recurrence, 6 years after the first treatment in The Norwegian Radium Hospital and 10 years after the first treatment for papilloma.

7. Man, 63 years of age with 2 pea-sized papillomatas. Biopsy: papilloma with moderate degree of atypia. Electro-coagulated. Free from recurrence $4^1/_2$ years.

All the patients had relatively well demarkated tumors, but regarding several of the cases we would possibly with our present indicative position have employed »open» electro-coagulation after cystotomy. (Cases nos. 2, 3, 4, and 6.) In 4 cases the microscopical diagnosis showed papillomatas with atypia. (Cases nos. 3, 4, 6 and 7.) The bits of tissue were, however, too small to determine infiltrating growth. Regarding one patient the biopsy was a failure (granulation tissue), and in one case the biopsy is missing, but in this instance there was evidence of a recurrence 4 years subsequent to electro-coagulation for a histologically verified carcinoma. Finally, in one case the histological examination showed infiltrating growth of highly atypical epithelium in a patient who is still alive free from recurrence after 10 years.

Regarding the 4 last mentioned patients who are still alive free from recurrence, cystotomy and electro-coagulation were performed and one of them had intubation of radium-needles in the wound bed. The morbid histories will also here be reported briefly.

8. Man, 56 years of age with 1 almond-sized and 1 pea-sized connective infiltration, as well as a polypoid tumor the size of a nut, all localized in the floor of the bladder. Biopsy from the three places revealed infiltrating growth of atypical epithelium. Diagnosis: Carcinoma. Cystotomy, electro-coagulation and post-operative roentgen-treatment. 10,000 r divided on 3 fields (2 frontal, and 1 perineal field). 6 months later an auxiliary dose of 1,700 r × 3 was given. Free from recurrence for $9^1/_2$ years.

9. Woman, 63 years of age with a tumour the size of a bean with a relatively small pedicle, localized behind the orifice of the left ureter. Cystotomy, electro-coagulation as well as intubation of 2 radium needles à 10 mgm. Radium Element for 24 hours. Post-operative roentgen treatment. 6,000 r divided on 2 fields. Biopsy: Papilloma with moderate atypia. Free from recurrence $2^1/_2$ years.

10. Man, 62 years of age with broad-based tumor the size of an egg, localized close to the orifice of the right ureter. Cystotomy followed by electro-coagulation made deep into the wall of the bladder, for which reason an intubation of radium needles was not considered justifiable. Biopsy: Infiltrating growth of poorly differentiated tumor tissue. Diagnosis: Carcinoma. Post-operative roentgen treatment given. Tumor-dose 3,284 r. Auxiliary dose of 1,000 r in tumor-dose was given 4 months later. Free from recurrence $2^1/_2$ years later.

11. Woman, 56 years of age with an almond-sized papillomatous tumor close to the orifice of the right ureter. Treatment: Cystotomy, electro-coagulation and post-operative roentgen therapy. 14,000 r divided on 4 fields. Radium was not intubated owing to the extreme thinness of the bladder wall. Biopsy: Infiltrating growth of highly atypical epithelium. Diagnosis: Carcinoma. Living, free from recurrence after $1^1/_2$ years, but has since been electro-coagulated twice for a small papilloma, last time half a year ago.

The first mentioned of these patients was treated before we had adopted the method of intubating radium in the wound-bed. He had an infiltrating carcinoma of the bladder and got post-operative roentgen treatment with a relatively low tumor-dose, and is still alive free from recurrence after $9^1/_2$ years. In 2 cases (nos. 10 and 11), where, in both instances, the histological examination revealed infiltrating growth of atypical epithelium, the intubation of radium was from prudential motives not employed, regarding the first case because the electro-coagulation had been made very deep into the bladder wall, in the second case due to the extreme thinness of the bladder wall. They are both living free from recurrence after $2^1/_2$ years and $1^1/_2$ years, respectively. Finally, in one case (no. 9) radium needles were intubated subsequent to electro-coagulation. As regards this patient who is living free from recurrence after $2^1/_2$ years, the histological examination revealed papilloma with moderate atypia. Electro-coagulation through the cystoscope has in this group accidentally proved successful in the majority of the patients who were free from symptoms. This fact of course does not permit us to draw the conclusion that this procedure may compete with »open» electro-coagulation, it being obvious that by means of the »open» method one may decide with far greater certainty the extension and depth of the necessary electro-coagulation to be performed, and in our opinion

this method ought to be preferred in the majority of the cases, even in the ones with small, well demarkated papillomatas, on condition that no counter-indication against cystotomy exists. Particularly in middle aged and older patients where these tumors clinically may manifest themselves as very malignant, even though the cystoscopic and histological picture is relatively benign, the patient ought at once to be subjected to the treatment which gives the greatest chance of radically destructing all tumor tissue. This question is indirectly illustrated by the progress of the disease in the 6 patients between the age of 40 and 60 years, who despite an apparently radical electro-coagulation and subsequent radiotherapy later have got intractable recurrences or are already dead. The 3 cases living with recurrence were all treated with cystotomy, electrocoagulation, intubation of radium and post-operative roentgen therapy. They had respectively: Broad based tumor the size of an almond (Biopsy: Carcinoma), hazelnut-sized pedicled tumor (Biopsy: Carcinoma), and tumor with narrow pedicle the size of a hazelnut (Biopsy: Papilloma with slight atypia.) The 3 patients who are dead from carcinoma of the bladder and received the same treatment, apart from the 1st one where intubation of radium needles was not administered, had respectively: Broad based tumor of hazelnut size, walnut-sized tumor (Biopsy showed in both cases papilloma) and the last had a nodular tumor the size of a Brazil-nut (Biopsy: Carcinoma). Thus, all 6 patients had small, well demarkated tumors which ought to have been well suited for the treatment administered. It is note-worthy that the histological examination in 3 of these cases revealed papilloma with atypia, in spite of the fact that the histologist had had for examination the entire tumor with its pedicle, and still they all got intractable recurrences after from 3 to 6 months. For this reason we interpret in middle aged and older patients a papilloma with atypia of the cells as a carcinoma, even though infiltrating growth of the epithelium is not manifest, and treat them on principle with cystotomy, electro-coagulation, radium intubation and post-operative roentgen therapy.

In the material we have been revising here, we have in all, 13 times carried out the combined method of surgical-radiological treatment with intubation of radium needles. During the last 2 years 12 new patients as well have received the same treatment. This number is of course still too small to permit us to decide how great a significance one may attribute to the supplement of radium needles to the usual treatment. However, we shall want to mention that at The Memorial Hospital in New York, where a similar treatment method is employed, the results achieved are as follows: 3 years symptom-freeness, approximately 50 % for the papillomatous carcinomas and 30 % when infiltrating growth of the epithelium exists.

At The Norwegian Radium Hospital we have unfortunately no experiences in the administration of Mc.Carthy's instrument and neither in the use of trans-urethral implantation of radium needles. It is possible, but hardly probable that by employing this method we might be able to treat larger tumors through the urethra.

The separate groups in our material are so far too small to allow a calculation of the percentages as regards the symptom-free. We will therefore content ourselves with looking at the total of the material and find that 115 of 155 patients are dead, 4 from intercurrent diseases and 111 from carcinoma of the bladder. We lack information on one patient. 39 are living, 11 of these with recurrence and 28 free from recurrence. Of 77 patients, 11 are living symptom-free with observation periods of more than 5 years (14.3 %) and 20 of 111, symptom-free with more than 3 years observation period (18 %).

It must be admitted that these results are very moderate. To this we would like to observe that our material is no example of what a consistent effectuation of surgical-radiological treatment in carcinoma of the bladder may yield at present, if the patient comes for treatment at the right time, and from the very first moment is treated at a special hospital of cancer. Patients with bladder tumors have, especially in the first years after The Norwegian Radium Hospital was opened, but also in the later years, to a great extent been admitted when the recurrences and the diffuse tumor infiltration have set in, that is, when the most favourable stage for the administration of the combined surgical-radiological treatment since long is passed. Finally, the principles in our treatment have been too heterogeneous because, as previously mentioned, our present lines of direction as regards the treatment, have only been consistently carried out for the last 4 to 5 years of the period of time which we have revised here.

To the chief of the hospital, ROLF BULL ENGELSTAD M. D., I should like to express my gratitude for his unfailingly kind advise and for his permission to use the hospital material.

SUMMARY

After a reference of the principles in the treatment of tumours of the urinary bladder, the author refers in detail 155 patients, 97 men and 58 women having been treated at The Norwegian Radium Hospital during the years 1932 to 1942. The general condition regarding 53 patients was so poor that even palliative roentgen treatment could not be administered.

Of 59 patients treated with roentgen, 14 became primary free from symptoms. Of these 8 are alive free from recurrence with observation periods of from 10 months to 7 years, 4 of whom with observation periods of more than 5 years. Of 35 patients primary surgically treated, with subsequent roentgen therapy, 13 are living free form recurrence

with observation periods of from 16 months to 10 years, 7 of whom with observation periods of more than 5 years. 39 of the total material are alive, 28 patients free from recurrence and 11 with recurrence. 115 are dead, 4 of intercurrent diseases, 111 of carcinoma of the bladder. Of 77 patients, 11 (14.3 %) are living symptom-free with observation periods of more than 5 years. Of 111 patients, 20 (18 %) are alive free from symptoms with observation periods of more than 3 years.

ZUSAMMENFASSUNG

Nach Wiedergabe der Grundsätze der Behandlung von Tumoren der Harnblase, berichtet Verf. eingehend über 155 Kranke, 97 Männer und 58 Frauen, die in den Jahren 1932—1942 im Norwegischen Radiumkrankenhause behandelt wurden. Der Kräftezustand war bei 53 Patienten so elend, dass nicht einmal palliative Röntgenbehandlung eingeleitet werden konnte.

Von 59 röntgenbehandelten Kranken wurden 14 primär symptomfrei. Von diesen leben 8 rezidivfrei nach einer Beobachtungszeit von 10 Monaten bis 7 Jahren, darunter 4 nach einer Beobachtungszeit von über 5 Jahren. Von 35 Kranken, die primär chirurgisch behandelt wurden mit darauffolgender Röntgenbehandlung, leben 13 rezidivfrei nach einer Beobachtungszeit von 16 Monaten bis 10 Jahren, darunter 7 nach einer Beobachtungszeit von über 5 Jahren. Vom Gesamtmaterial leben 39 Patienten, 28 rezidivfrei und 11 mit Rückfällen. 115 sind gestorben, 4 an interkurrenten Krankheiten, 111 an Harnblasenkrebs. Von 77 Kranken leben 11 (14.3 %) symptomfrei nach einer Beobachtungszeit von über 5 Jahren. Von 111 Kranken leben 20 (18 %) symptomfrei nach einer Beobachtungszeit von über 3 Jahren.

RÉSUMÉ

Après s'être référé aux principes du traitement des tumeurs vésicales, l'auteur fait un rapport détaillé sur 155 malades, 97 hommes et 58 femmes, qui ont été traités à l'Hôpital Norvégien du Radium de 1932 à 1942. L'état général de 53 malades était si mauvais que l'on n'a même pas pu appliquer le traitement radiologique palliatif.

De 59 malades traités aux rayons de roentgen, 14 ont été guéris de leurs symptômes primaires. De ceux-ci 8 sont en vie sans récidive au cours d'un temps d'observation variant de 10 mois à 7 ans; pour 4 d'entre eux, le temps d'observation dépasse 5 ans. De 35 malades qui ont été opéré et traités aux rayons de roentgen après l'opération, 13 sont en vie sans récidive avec des périodes d'observation variant de 16 mois à 10 ans. Pour 7 d'entre eux, les périodes d'observation dépassent 5 ans. Du nombre total, 38 sont en vie, 28 sans récidive et 11 avec récidive. 115 sont décédés, 4 de maladies intercurrentes, 111 de carcinome de la vessie. De 77 malades, 11 (14.3 %) sont vivants et sans symptômes avec période d'observation dépassant 5 ans. De 111 malades, 20 (18 %) sont vivants et sans symptômes avec période d'observation dépassant 3 ans.

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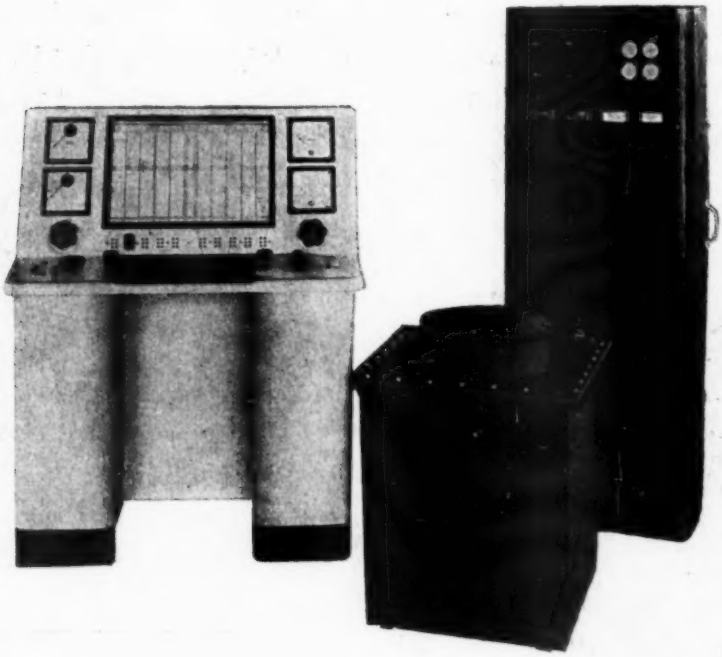

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